A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND SEVERITY OF ACUTE ISCHEMIC STROKE IN PATIENTS ADMITTED IN GOVT KILPAUK MEDICAL COLLEGE HOSPITAL,CHENNAI

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In Partial Fulfillment of the Regulations

For the Award of the Degree of

M.D.(GENERAL MEDICINE)- BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE
CHENNAI
APRIL – 2015

BONAFIDE CERTIFICATE

This is to certify that the Thesis "**A Study on Correlation between Serum Cortisol and Severity of Acute Ischemic Stroke in patients admitted in Govt Kilpauk Medical College Hospital, Chennai"** is a genuine work done by **Dr. T. ALLWYN YABESH,** Post Graduate Student in the Department of Medicine, Government Kilpauk Medical College under the guidance of **PROF. DR. R. SABARATNAVEL M.D.,** Head of the Department, Department of Medicine, Kilpauk Medical College.

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ACKNOWLEDGEMENT

I would like to thank my beloved Dean, Kilpauk Medical College **Prof. Dr. N. Gunasekaran M.D., DTCD.,** for his kind permission to conduct the study in Kilpauk Medical College.

I would like to acknowledge **Prof. Dr. R.Sabaratnavel M.D.,** Professor and Head of the Department of Medicine, Kilpauk Medical College for his supportiveness and guidance to my study work.

I would like to acknowledge **Prof. Dr. T. Ravindran M.D., DNB., Dip Diab.,** my unit chief for his support and guidance during the course of the study.

I would like to show my gratitude to the Professor of Medicine **Dr. Ushalakshmi M.D.,** for her guidance and support.

I would like to show my gratitude to **Prof. Dr. Arunan M.D., D.M.,** Professor and Head of the Department of Neurology for his supportiveness and guidance to my study work.

I am very grateful to **Dr. Paneerselvam M.D., Dr. Rajan Babu M.D., D.M., Dr. Murugapandiyan M.D., D.M.,(Neurology)** my Assistant Professors for their guidance and support.

I am also grateful to my parents for their moral support in finishing this thesis. Finally I would like to owe a lot to my patients for their support and without them this project would not be possible.

DECLARATION

I **Dr. T. ALLWYN YABESH** solemnly declare that the dissertation titled "**A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND SEVERITY OF ACUTE ISCHEMIC STROKE IN PATIENTS ADMITTED IN GOVT KILPAUK MEDICAL COLLEGE HOSPITAL,CHENNAI"** has been prepared by me. This is submitted to the Tamil Nadu Dr. M.G.R. Medical University Chennai in partial fulfillment of the requirement for the award of MD degree Branch I (General Medicine)

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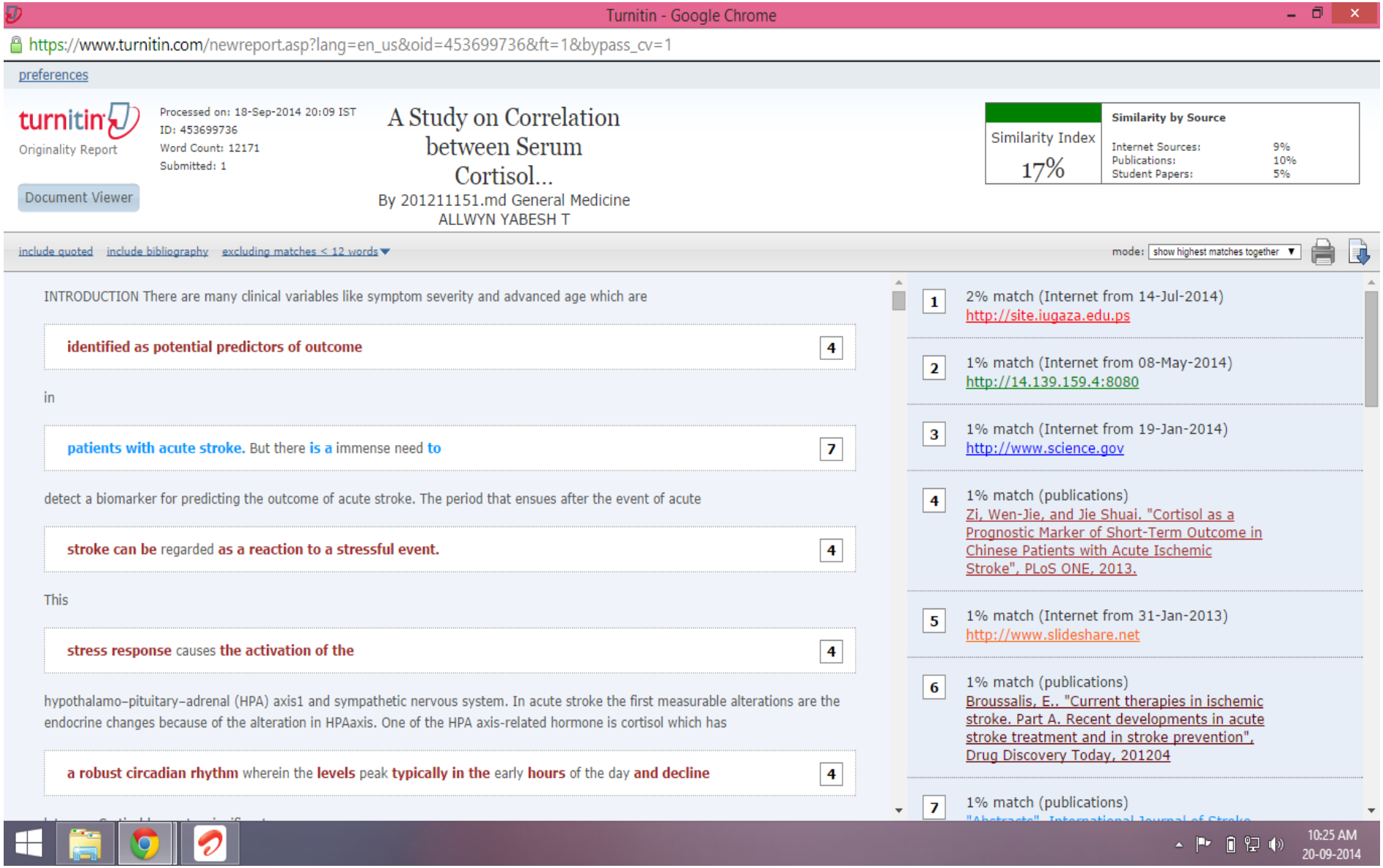
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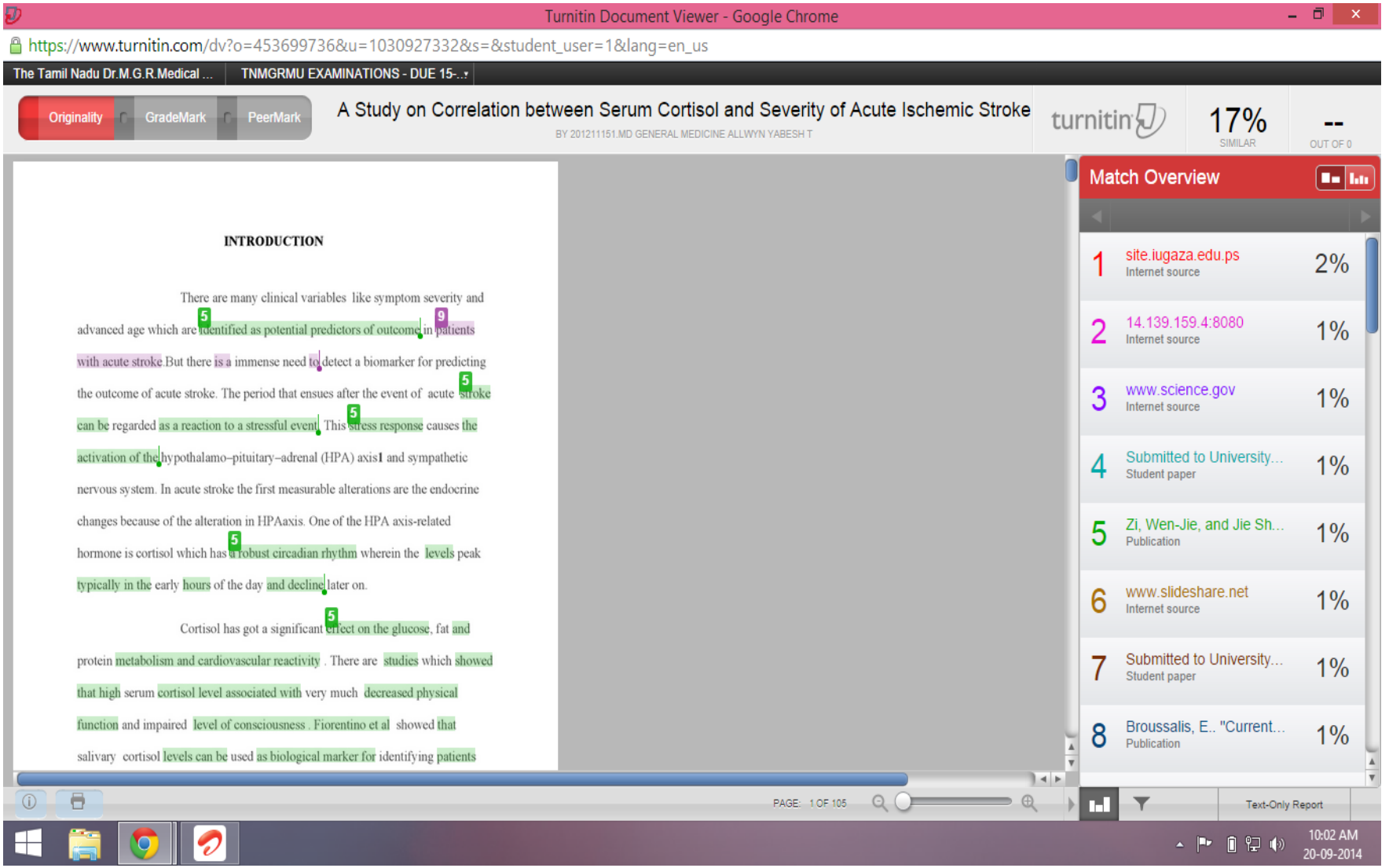
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Cortisol has got a significant effect on the glucose, fat and protein metabolism and cardiovascular reactivity . There are studies which showed that high serum cortisol level associated with very much decreased physical function and impaired level of consciousness . Fiorentino et al showed that salivary cortisol levels can be used as biological marker for identifying patients
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A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND SEVERITY OF ACUTE ISCHEMIC STROKE IN PATIENTS ADMITTED IN GOVT KILPAUK MEDICAL COLLEGE HOSPITAL,CHENNAI

ABSTRACT:

INTRODUCTION:

There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke.But there is a immense need to detect a biomarker for predicting the outcome of acute stroke. The stress response that occurs after the event of acute stroke causes the activation of the hypothalamo–pituitary–adrenal (HPA) axis. Certain studies have found that increased serum cortisol level in patients with acute stroke is related to larger infarct volume, greater stroke severity and poor outcome, including death

AIM AND OBJECTIVE:

To assess the relationship of single serum cortisol levels to the severity of acute ischemic stroke.

MATERIALS AND METHODS:

About 50 new cases of acute ischemic stroke patients, within 72 hours of the acute neurological event , who were admitted in the Kilpauk Medical College Hospital were included in the study.The study was conducted for a period of 6 months.CT Brain was taken during admission to confirm acute ischemic stroke.NIHSS (National Institute of Health Stroke Scale)score for all the patients were assessed for severity at the time of admission.Serum cortisol levels were measured on the next day early morning. After 15 days, the functional outcome of the patients were assessed using Modified Rankin Scale. Correlation between serum cortisol levels and stroke scales are assessed by Chi – Square Test.All statistical analysis are performed using SPSS (software package used for statistical analysis) package.

RESULTS:

Of the 50 cases, serum cortisol level of 23 cases were within normal limits(</=690nmol/L) of which 65.2% had NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6 .As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol level had no major stroke. Remaining 27 cases had elevated serum cortisol levels.100% of the cases with serum cortisol level of more than 690nmol/L had NIHSS score above 6.With the p value of <0.001 this is found to be statistically significant. As the

NIHSS score above 6 is considered to be moderate to severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol level had moderate to severe stroke. Of the 50 cases, serum cortisol levels of 23 cases were within normal limits(,/=690nmol/L)of which 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3.Since MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favourable outcome ,it is clear from the above findings that most of the cases with normal serum cortisol had a favourable outcome with minimal neurological impairment. And in the remaining 27 cases which had serum cortisol level more than 690 nmol/L, 3.7% had MRS score of less than or equal to 3 and 96.3% had MRS score of more than 3.With the p value of <0.001, this is statistically significant .Since MRS score more than 3 is associated with bad outcome, most of the cases with elevated serum cotisol had a poor outcome with severe neurological impairment.

CONCLUSION:

Among the patients with acute ischemic stroke ,high serum cortisol levels at the time of admission correlates with,

1.Clinical severity which is assessed by National Institute of Health Stroke Scale and

2.Poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale

KEY WORDS:

Acute ischemic stroke, HPA axis, serum cortisol, clinical severity,Functional outcome, stroke scales

INTRODUCTION

There are many clinical variables like symptom severity and advanced age which are identified as potential predictors of outcome in patients with acute stroke.But there is a immense need to detect a biomarker for predicting the outcome of acute stroke. The period that ensues after the event of acute stroke can be regarded as a reaction to a stressful event. This stress response causes the activation of the hypothalamo–pituitary–adrenal (HPA) axis[1] and sympathetic nervous system. In acute stroke the first measurable alterations are the endocrine changes because of the alteration in HPAaxis. One of the HPA axis-related hormone is cortisol which has a robust circadian rhythm wherein the levels peak typically in the early hours of the day and decline later on.

Cortisol has got a significant effect on the glucose[2], fat and protein metabolism and cardiovascular reactivity. There are studies which showed that high serum cortisol level associated with very much decreased physical function and impaired level of consciousness . Fiorentino et al showed that salivary cortisol levels can be used as biological marker for identifying patients who are prone for acquiring lower benefits from inpatient rehabilitation services. It is also proved in many studies that , increased cortisol concentrations have been observed in acute ischemic stroke and SAH. Certain studies have found that

increased serum and urinary cortisol level[3] in patients with acute stroke is related to larger infarct volume, greater stroke severity and poor outcome[4,5], including death. After the acute event , increased serum cortisol level is significantly associated with acute confusional state .

The primary objective of this study dissertation is to test the hypothesis that increased single serum cortisol level is associated with increased severity of acute ischemic stroke. Though cortisol level has diurnal variations it has been showed that the normal circadian rhythm of cortisol is suspended during acute stroke and there is no variation of cortisol level in serum throughout the day due to perturbations in the HPA axis.

AIM OF THE STUDY:

To assess the relationship of single serum cortisol levels to the severity of acute ischemic stroke.

JUSTIFICATION OF THE STUDY:

Early prediction of outcome is important for allocation of therapeutic strategies. Endocrine alterations of the hypothalamus–pituitary–adrenal axis are one of the first stress-induced alterations after cerebral ischemia. We therefore evaluated the serum cortisol levels in assessing the severity of acute ischemic stroke.

Studies that are conducted by *Wen Jie Zi & Jie Shuai* on Cortisol as a Prognostic Marker of Short-Term Outcome in Chinese Patients with Acute Ischemic Stroke showed that Cortisol can be seen as an independent short-term prognostic marker of functional outcome and death in Chinese patients with acute ischemic stroke even after correcting confounding factors. Combined model can add significant additional predictive information to the clinical score of the NIHSS.

REVIEW OF LITERATURE

CORTISOL:

STRUCTURE OF CORTISOL:

Cortisol is the very potent glucocorticoid and it represents 95 percent of the entire glucocorticoid activity. It is the hormone of the adrenal cortex and it is secreted in the zona fasciculata and zona reticularis, however the former plays a major role in synthesizing this hormone.Cortisol is the derivative of cholesterol.It contains the cyclopentanoperhydrophenanthrene nucleus.It is a C21 steroid and has a Delta^4-3-keto configuration in the A ring, with 17 hydroxy groups at carbon numbers 11 and 21

BIOSYNTHESIS OF CORTISOL:

Cholesterol is the precursor of all the steroids.Most of the cholesterol is derived from LDL which is present in the circulation. However some of the cholesterol is produced from the acetate.Adrenocortical cells have rich supply of LDL receptors.After the cholesterol is esterified it is contained in lipid droplets.In the lipid droplets the formation of free cholesterol is catalysed by Cholesterol ester hydrolase. Sterol carrier protein transports the cholesterol to mitochondria.

The cholesterol desmolase or side chain cleavage enzyme is also known as P450scc or CYP11A1 is a member of cytochrome P450 superfamily, which catalyses the conversion of cholesterol to pregnenalone.This reaction takes place in the mitochondria

Pregnenalone enters the smooth endopasmic reticulum and it forms progesterone by dehydrogenation which is catalysed by 3 beta hydroxysteroid dehydrogenase. The special feature of the enzyme 3 beta hydroxysteroid dehydrogenase is that it does not belong to the cytochrome P450 superfamily and has a molecular weight of 46000.

Hydroxylation of the progesterone to 11- deoxycorticosterone and of 17 alpha hydroxyprogesterone to deoxycortisol occurs in the smooth endoplasmic reticulum. 21beta –hydroxylase otherwise called as P450c21 or CYP21A2 which belongs to the cytochrome P450 superfamily, catalyses the above reaction.

11-deoxycorticosterone and 11-deoxycortisol enters the mitochondria. 11beta- hydroxylase which is otherwise called as P450c11or CYP11B1 , belongs to the cytochrome P450 superfamily . This enzyme catalyses the conversion of 11-deoxycorticosterone to corticosterone and 11- deoxycortisol to cortisol. This occurs in the zona fasciculata and zona reticularis of the adrenal cortex. Steroidogenesis thus involves the frequent shuttling of substrates into and out of mitochondria

ACTH binds to the high affinity receptors of the adrenocortical cell plasma membranes. This activates the adenylyl cyclase through Gs.Downstream the activation of the adenylyl cyclase there is the prompt increase in the synthesis of pregnenalone and its derivatives with secretion of the latter.

However adrenal steroidogenesis can be impaired in sepsis due to release of inflammatory cytokines[13]

SYNTHESIS OF CHOLESTEROL

Cholesterol

↓ *Cholesterol desmolase*

Pregnenalone

↓ *17- alpha hydroxylase*

17- hydroxyl pregnenalone

↓ *3-beta hydroxysteroid dehydrogenase*

17- hydroxyl progesterone

↓ *21- hydroxylase*

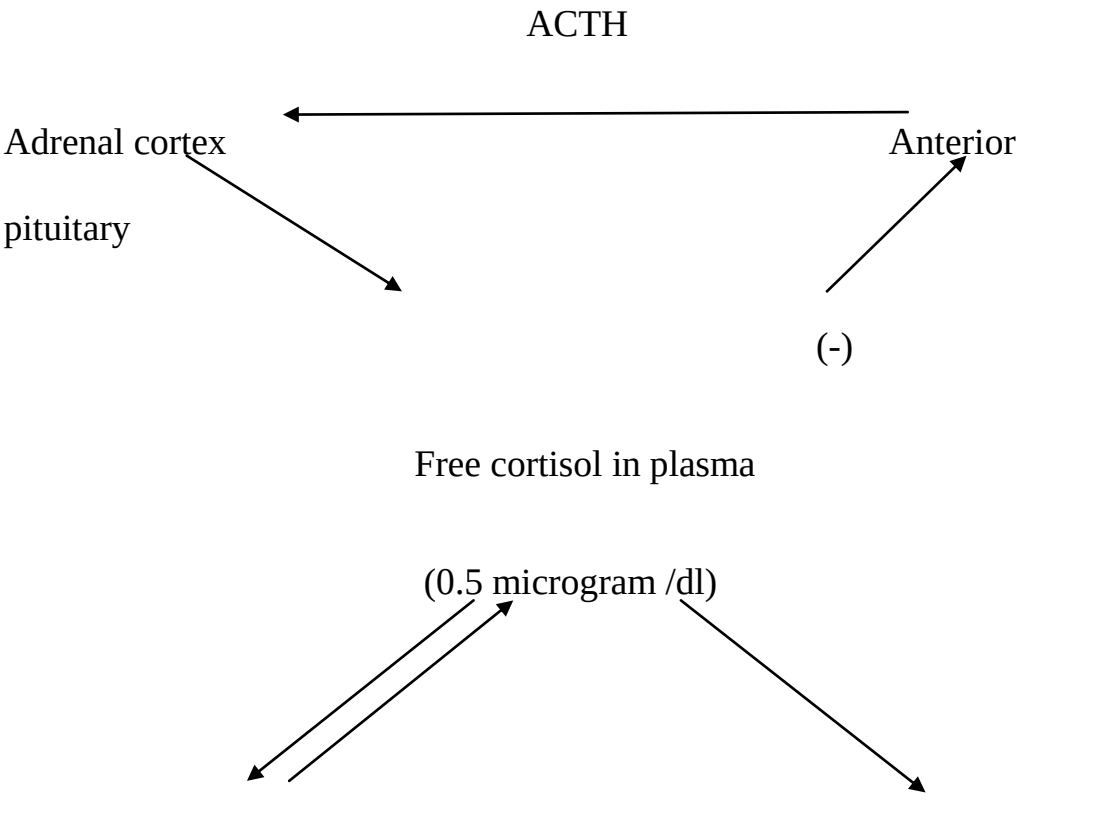
11- deoxy cortisol

↓ *11- beta hydroxylase*

Cortisol

TRANSPORTATION OF CORTISOL:

Corticosteroid binding globulin or alpha globulin binds to cortisol in the circulation. Cortisol also binds to albumin to a lesser degree. Corticosterone also binds similarly but to a lesser degree. The cortisol has a half life of about 60 to 90 minutes which is comparatively longer than corticosterone which has a half life of about 50 minutes. Bound steroids are however physiologically inactive forms. Because of protein binding only little free cortisol and corticosterone is found in the urine.



The above flowchart depicts the equilibrium between cortisol and its binding protein and the implications of binding in terms of tissue supplies and ACTH secretion.There is a constant supply of free cortisol that is made available to the tissues as the bound cortisol functions as a circulating reservoir of hormone.

At normal levels of total plasma cortisol (13.5microgram/dl or 375 nmol/L), very less amount of cortisol is present in the plasma , however the binding sites of Cortisol binding globulin (CBG) becomes saturated when the total concentration of pasma cortisol raises above 20 microgram/dl. At higher Plasma concentrations of cortisol levels, tendency to bind with albumin increases, but the major increase is in the unbound fraction.

Liver synthesizes the cortisol and estrogen increases its production. The levels of Cortisol Binding Globulin is increased during pregnancy. The levels are decreased[8] in conditions like cirrhosis of liver, nephrosis and multiple myeloma.

When the CBG levels increases, more of the cortisol is bound.The free cortisol levels initially drops. ACTH is stimulated by this event and more cortisol is secreted until a new equilibrium is achieved at which the bound cortisol is elevated but the free cortisol is normal.

Changes in the opposite direction occurs when the CBG levels falls.This explains why pregnant women have high total plasma cortisol levels without the symptoms of glucocorticoids excess and conversely why the patients with nephrosis have low total plasma cortisol without symptoms of glucocorticoid deficiency.

METABOLISM OF CORTISOL:

Major site of metabolism of cortisol is Liver. Most of the cortisol is reduced to dihydrocortisol. Which is then converted to tetrahydrocortisol. Later it is conjugated to glucuronic acid.This reaction catalysed by glucuronyl transferase system.It also catalyses the formation of glucoronides of bilirubin and a number of hormones and drugs. Notably there is a competitive inhibition occurring between these substrates for the enzyme system..

There are atleast two forms of the enzymes 11 – beta hydroxyl steroid dehydrogenase which is present in liver and other tissues.Type1 catalyses both the conversion of cortisol to cortisone and the reverse reaction , though the major function of this enzyme is to act as reductase, forming cortisol from corticosterone. However type 2 catalyses the conversion of cortisol to cortisone only.

Cortisone is an active glucocorticoid because it is converted to cortisol and it is well known because of its extensive application in medicine.It is not secreted in appreciable quantity in adrenal glands.

Tetrahydroglucoronide derivatives of cortisol and corticosterone are freely water soluble. They do not bind with the protein after entering into the circulation. Partly, by means of tubular secretion, they are rapidly excreted in the urine.

In the liver about 10 percent of the secreted cortisol is converted to the 17 ketosteroid derivatives of cortisol and cortisone.The ketosteroids are excreted in the urine after being conjugated for the most part to sulfate. Other metabolites including the 20- hydroxyl derivatives are formed.

Part of the cortisol also enters the entero hepatic circulation. About 15 percent of the secreted cortisol is excreted in the stool. The metabolism of corticosterone is similar to that of cortisol except that it does not form a 17- ketosteroid derivative.

The rate of hepatic inactivation of glucocorticoids is depressed in conditions like liver disease, surgery and stresses.Thus in stressed humans the plasma free cortisol levels rises higher than it does with maximal ACTH stimulation in the absence of stress.

REGULATION OF CORTISOL SECRETION:

ROLE OF ACTH:

The basal secretion of the cortisol and the stress provoked increased secretion are both under the dependency of ACTH from the anterior pituitary. In addition to the prompt increase in the secretion of the cortisol , ACTH also causes increased responsiveness of the adrenal gland to the subsequent doses of ACTH.

CIRCADIAN RHYTHM:

The plasma cortisol tend rise and fall in response to the secretion of ACTH which occurs in irregular bursts throughout the day.In early morning , the bursts are more frequent and between 4AM and 10AM occurs the 75% of the daily production of the cortisol.This diurnal rhythm in the secreting pattern of ACTH is seen in patients with adrenal insufficiency receiving constant doses of the glucocorticoids.The biologic clock responsible for the diurnal ACTH secretion is situated in the suprachiasmatic nuclei of the hypothalamus. If the day is lengthened experimentally to more than 24 hours, then the adrenal cycle also lengthens , but the rise of ACTH secretion occurs during the period of sleep.

THE RESPONSE TO STRESS:

Morning plasma ACTH levels in a healthy resting human is about 25pg/ml. The amount of ACTH produced exceeds the amount necessary to produce maximal cortisol output , during the times of severe stress[6].

In emergency situations, the increase in ACTH secretion is mediated through the hypothalamus by the release of Corticotrophin Releasing Hormone(CRH).The neurons in the paraventricular nuclei produces this polypeptide and is secreted in the median eminence. Then it is transported to the anterior pituitary through the portal hypophyseal vessels, where it stimulates ACTH secretion.Increased secretion in response to various stresses is blocked if the median eminence is destroyed.

Paraventricular nuclei is the place of convergence for many afferent nerve pathways from many parts of the brain.Increase in ACTH production in response to the fear,anxiety, apprehension, emotional stresses are mediated by the fibres from the amygdaloid nucei. The drive for the diurnal rhythm is provided by the input from the suprachiasmatic nuclei.

Impulses ascend to the hypothalamus through the nociceptive pathways and the reticular formation trigger increased ACTH secretion in response to injury.Inhibitory input is triggered by the baroreceptors via the nucleus of tractus solitarius.

CORTISOL FEEDBACK:

ACTH secretion is inhibited by the free glucocorticoid levels.The degree of the pituitary inhibition is proportional to the circulating cortisol levels.At both the levels of pituitary and hypothalamus the inhibitory effect is exerted.The inhibition is due primarily to an action on DNA and the maximal inhibition takes several hours to develop, although more rapid fast feedback do occurs.The glucocorticoid potency parallels the ACTH inhibiting activity of various steroids.

The rate of ACTH secretion is determined by the summation of two opposing forces. The sum of the neural and possibly other stimuli converging through the hypothalamus to increase ACTH secretion , and the magnitude of the braking action of glucocorticoids on ACTH secretion, which is proportionate to their level in the circulating blood.

PHYSIOLOGICAL EFFECTS OF CORTISOL:

MECHANISM OF ACTION:

The multiple of functions of the cortisol is exerted through the binding of cortisol to the glucocorticoid receptors . The steroid receptor complex then act as transcription factors and promote the transcription of certain DNA segments. Other proteins in the cell called transcription factors are also necessary for the hormone receptor complex to interact appropriately with the glucocorticoid response elements.

Cortisol increases or decreases many of the genes to alter the synthesis of mRNA for the protein that mediate the multiple physiologic effects. Thus the physiologic effects of cortisol are not immediate but require 45- 60 minutes for the proteins to be synthesized and upto several hours to days to fully develop. In addition , the cortisol has non genomic actions as well.

EFFECTS ON INTERMEDIARY METABOLISM:\

CARBOHYDRATE METABOLISM:

Cortisol can increase the rate of gluconeogenesis by 6 to 10 folds by two following mechanisms,

1. Cortisol increases the enzymes in the liver which converts the amino acids to glucose.In the liver cell nuclei, cortisol, activates DNA transcription resulting in formation of messenger RNAs which in turn produces the array of enzymes required for gluconeogenesis.
2. Cortisol causes mobilization of the amino acids from the extrahepatic tissues mainly muscles. As a result more amino acids will be available in the plasma to enter into the gluconeogenesis process of the liver and thereby to promote the formation of glucose.

One of the effects of increased gluconeogenesis is the elevated glycogen storage in the cells of liver. This effect of cortisol allows the other glycolytic hormones like epinephrine and glucagon to mobilize glucose in times of need , such as between meals.

Cortisol also causes a moderate decrease in the rate of glucose utilization by most cells in the body.A suggested mechanism is based on the fact that cortisol depress the oxidation of NADH to form NAD+. Because NADH must be oxidized to allow glycolysis, this effect could account for the diminished use of glucose by the cells.

The above factors causes the blood glucose to rise, which in turn stimulates the secretion of insulin. The increased insulin levels , however , are not as effective in maintaining the plasma glucose levels as during normal conditions.

Also high levels of cortisol reduces the sensitivity of many tissues especially skeletal muscles and adipose tissues to the stimulatory effect of insulin on glucose uptake and utilization.The reason for the impaired sensitivity to insulin by the tissues is that the high level of fatty acids caused by the effect of cortisol by mobilising lipids from fat depots.The increase in the blood glucose is occasionally great enough (50 percent or more above normal) that the condition is called adrenal diabetes. Administration of insulin lowers the blood glucose levels only to a moderate amount in adrenal diabetes because the tissues are resistant to the insulin effects.

PROTEIN METABOLISM:

Cortisol causes reduction of proteins in all the tissues except in liver.This is achieved by two factors:

1. Decreased synthesis of protein

2. Increased protein catabolism in the tissues

Especially in muscle and lymphoid tissue it causes reduced synthesis of m RNA and hence subsequent synthesis of proteins . Also it causes reduced transport of amino acids into extrahepatic tissues.

The muscle can become so weak in the presence of increased amount of cortisol and the individual cannot even rise from the squatting position. Also the immunity of the lymphoid organ can be reduced to a small fraction of normal.

Contrary to the reduced protein elsewhere in the body, in the liver there is increased amino acid transport and stimulation of liver enzymes for the synthesis of protein, and the liver produces increased amount of plasma protein which is released into the blood.

Cortisol has the following effect on protein metabolism:

1. Deamination of the amino acids by the liver is increased
2. Synthesis of protein is increased in the liver
3. Plasma proteins synthesis is increased in liver
4. Stimulation for conversion of amino acids to glucose and so there is enhancement of gluconeogenesis

FAT METABOLISM:

Cortisol promotes fatty acid mobilization from the adipose tissue and enhances the concentration of fatty acids in the plasma. And also increases their energy utilization.Cortisol has direct effect on oxidation of fatty acids in the cells. Cortisol achieves the above effect by the following mechanism. It reduces the transport of glucose into the fat cells. Alpha –

glycerophosphate is required for the deposition and subsequent maintenance of triglycerides in the fat cells, while in its absence the fatty acids are released from the adipose tissue.

In times of stress and starvation the energy is derived from the utilization of fatty acids instead of glucose by increased mobilization of fatty acids and increased oxidation of fatty acids by cortisol. However it takes several hours for the effect of cortisol to be fully pronounced and it is not so fast or robust which is expected in a similar shift promoted by decrease in insulin.By the utilization of fatty acids it conserves glucose and glycogen for long term utility.

Also the cortisol causes deposition of fat around chest and head giving the appearance of moon facies and buffalo like torso due to the fact that some part of the body exhibit fat generation more rapidly than it is mobilized and oxidized .

WATER METABOLISM:

Cortisol reduces the plasma vasopressin levels and hence restores plasma volume and increases the glomerular filtration rate and prevents water intoxication. This is evident in the treatment of adrenal insuffiency with glucocorticoids.

PERMISSIVE ACTION:

Minimal amounts of cortisol must be present for good number of metabolic reactions to take place . But cortisol do not produce these reactions by themselves. This is called permissive action. Following are the examples for such permissive actions.

1. For glucagon and catecholamine to exihibit their calorigenic effects
2. Lipolytic effects of catecholamines
3. Pressor responses of catecholamines
4. Bronchodilation by catecholamines

EFFECT ON CNS:

Cortisol reverses the changes in central nervous system that occurs in adrenal insufficiency, which includes the appearance of slower rhythm in EEG.Also it causes personality changes which include irritability, loss of concentration and apprehension.

EFFECT ON HEMATOPOIETIC CELLS:

Cortisol increases the sequestration of eosinophils in lungs and spleen.Thereby it reduces the amount of eosinophils that are circulating.

It also reduces the basophils in the circulation.However cortisol increases the neutrophils, platelets and red blood cells.

It inhibits lymphocyte mitotic activity. Also it reduces the size of lymph nodes. It decreases the count of circulating lymphocytes.Cortisol inhibits the NF-kB on the nucleus, thereby it reduces the secretion of cytokines that play a pivotal role in inflammation.

There is reduced multiplication of lymphocytes due to reduced secretion of Interleukin-2 and these cells undergo apoptosis.

ACTION ON OTHER HARMONES:

Cortisol in large amounts inhibits growth by decreasing growth hormone secretion. Cortisol decreases TSH secretion.The maturation of surfactant in the lungs is accelerated by cortisol during foetal life.

ROLE OF CORTISOL IN STRESS AND INFLAMMTION:

Any type of stress be it neurogenic or physical, stimulates the anterior pituitary to secrete ACTH which in turn increases the adrenocortical secretion of cortisol within minutes.Cortisol release is increased by following types of stress.Infection

1. Trauma
2. Intense heat

3. Intense cold
4. Injection of sympathomimetic drugs
5. Surgery
6. Injection of necrotizing substances beneath the skin
7. Almost any debilitating disease

By the fast mobilization of fats and amino acids by cortisol, it helps the damaged tissues to utilize them for energy and synthesis of new proteins and other essential substances like pyramidines, purines and creatine phosphate, that are essential for reproduction and maintenance of cells.

Also it is surprising that cortisol do not mobilize basic functional proteins that are present in the cells, like proteins of neuron, contractile proteins of the muscle , until all other proteins are mobilized.The effect of cortisol is thus preferential in mobilizing the proteins that are labile to make amino acids available for the cells that are in need to produce substances necessary for life.

Inflammation includes five main stages:

1. Bradykinin,prostaglandin ,histamine and other proteolytic enzymes are released from the site of injury that activates the inflammatory process.

2. Erythema, caused by increased blood flow to the site of inflammation by the above released products.

3. Non pitting type of edema, caused by the large amount of plasma leaking out of capillaries due to increased permeability of capillaries which is followed by clotting of the tissue fluid.

4. Leukocytic infiltration around the inflamed area.

5. Ingrowth of fibrous tissue, after days or weeks.

Cortisol exerts anti inflammatory effect by three ways:

a) Early stages of inflammation is blocked even before the inflammation begins

b) Rapid resolution of inflammation if it has begun already

c) Increased rapidity of healing

MEASUREMENT OF CORTISOL:

Cortisol can be measured in heparinised plasma or serum. It can also be measured in urine. Cortisol analysis in saliva can be used as a surrogate marker for its measurements in plasma or serum.

PRECAUTIONS IN SAMPLING AND HANDLING:

During venepuncture stress should be minimized for cortisol measurement to avoid spurious rise of serum cortisol.In salivary samples, it should be frozen to precipitate salivary glycoproteins to leave a non viscous fluid.

LIMITATIONS:

There are limitations for the diagnostic utility of the single cortisol measurement, which are due to,

1. Diurnal variation in cortisol concentration
2. Cortisol elevation during stress
3. Episodic cortisol secretion

Stress can make the cortisol levels in patients with adrenal insufficiency to fall within reference range, similarly, patients with

cushings disease can have normal values of cortisol levels ,despite loss of diurnal variation, during the day.

ANALYTICAL METHODS:

a) Chromatographic method: It has the advantage of specificity. It distinguishes cortisol from metabolites and steroids.It needs sample processing before analysis and is labour intensive.

b) Immunoassay: This is the most frequently employed method. From the binding protein cortisol is quantitatively displaced and using antibodies, it is measured immunometrically, which are specific to cortisol.

CROSS REACTIVITY:

There can be interfering substances that can cause cross reactivity like, prednisone, methyl prednisolone and prednisolone.

REFERENCE CORTISOL VALUES:

From 8.00 am to 12 noon - 138–690 nmol/L

From 12 noon to 8 pm - 138–414 nmol/L

From 8.00 pm to 8.00am - 0–276 nmol/L

DIAGNOSTIC TESTS FOR CORTISOL EXCESS:

Dexamethasone suppression test is employed to diagnose cortisol excess.Suppression of CRH/ACTH by dexamethasone ,in turn suppresses cortisol.If the production of cortisol is autonomous , dexamethasone has only little additional effect as the ACTH is already suppressed.Dexamethasone suppression test is ineffective in low doses,as in ACTH producing pituitary adenoma, but induces suppression, usually at high doses. Thus dexamethasone suppression test helps to diffenrentiate the causes of cortisol excess.

DIAGNOSTIC TESTS FOR CORTISOL DEFICIENCY:

ACTH stimulation of cortisol production is employed for assessing the deficiency of cortisol.Administration of cosyntropin(ACTH1-24), 0.25mg im/iv is involved in standard ACTH stimulation test.At 0, 30, 60 minutes blood samples are tested for cortisol. A cortisol level of more than 20 microgram /dl or >10microgram /dl increment over baseline is considered as normal response.To avoid overstimulation of adrenal gland, low dose cosyntropin test is used where only 1 microgram of cosyntropin is given intravenously.

Also adrenal insufficiency is tested by insulin tolerance test(ITT).The hypothalamic CRH release is triggered by insulin induced

hypoglycemia, which activates entire HPA axis.Blood samples are collected at 0, 30, 60, 120 minutes and tested for glucose, growth hormone and cortisol after injecting 0.1 U /kg of insulin intravenously. After the patient achieves symptomatic hypoglycemia(glucose<40mg/dl) oral or IV glucose is administered. Cortisol more than 20 microgram/dl and growth hormone more than 5.1microgram/L is considered as a normal response.ITT is contraindicated in cerebrovascular accidents, coronary artery disease or seizure disorders. Hence the commonly accepted first line test is short cosyntropin test.

STROKE

DEFINITION:

A stroke is defined as abrupt onset of neurological deficit which is attributable to a focal vascular cause lasting for more than 24 hours. Reduction in blood flow lasting for more than several seconds causes cerebral ischemia. Infarction or death of a brain tissue ensues, if the blood flow cessation lasts for more than few minutes.

When all neurological symptoms and signs resolve within 24 hours, the condition is termed as Transient Ischemic Attack.Focal ischemia is caused by either a emboli from a arterial source which is proximal or from heart or due to thrombosis of major cerebral vessels. Intracranial hemorrhage is caused by bleeding into brain parenchyma and producing mass effects leading to manifestation of neurological symptoms.

EPIDEMIOLOGY:

The community based study on stroke was first conducted in and around vellore during 1969-1971.Then during 1971-1974 , a study was conducted in Rohtak in North India[15.] On comparison with Caucasians and Chinese , the prevalence of stroke is lower among the population of india. The age adjusted prevalence rate of stroke was 250-350/100000.It is ascertained that the mortality due to stroke is only 1.2% when

compared to other causes. The proportion of death due to stroke is increased with age. The gender ratio of death due to stroke is 1[14]

RISK FACTORS FOR STROKE:

NON MODIFIABLE RISK FACTORS:

AGE:- Age is the most important risk factor for stroke .The rate of stroke doubles in men and women , for every successive 10 years after the age of 55.

SEX: The incidence of stroke is 1.25 times more in men when compared to women. However because women live longer than men, more women die of stroke than men.

RACE:- The mortality rate of stroke is higher in blacks[20] than whites. Mortality rates are 4 to 5 times higher for African – Americans when compared with whites, between the age group of 45 and 55 years. This difference decreases as the age advances. Asians especially Japanese and Chinese have very high incidence rates of stroke, also the intracranial atherosclerosis is more common in Chinese.[14]

HEREDITY:- There is a increased tendency of stroke to run in families because of genetic tendency of stroke, genetic determination of risk factors for stroke, common familial exposure to lifestyle and environmental risks

MODIFIABLE RISK FACTORS:

HYPERTENSION: The relative risk of stroke is 4 when an individual is said to have a hypertension. The hypertension is strong risk factor for stroke[14-16].The odds ratio for the age of 50 is 4 whereas for the age of 90 is 1.In a study of 50000 patients around the world with 17 treatment trials of hypertension, there is 40 % reduction of fatal stroke and 38% reduction in all stroke, favouring treatment of hypertension. Treatment of systolic hypertension with antihypertensives in elderly persons is very effective in preventing stroke

CARDIAC DISEASE: Atrial fibrillation is one of the powerful risk factor of stroke[24]. With increase in age the incidence and prevalence of atrial fibrillation increases. It was proved in Framingham study that the attributable risk of AF for stroke increased from 1.5% in individuals who are aged 50 to 59 years to 23.5% in subjects of age 80 to 89 years. It is proved that nearly half of the cardio embolic strokes occur due to atrial fibrillation. In a pooled analysis of AF trials warfarin anticoagulation reduces the stroke risk by 68%.

Cardiac valve abnormalities like mitral valve prolapse and mitral stenosis increases the risk of incidence of stroke. Another risk factor for stroke is mitral annular calcification. The risk of stroke increases five fold with both AF and mitral annular calcification.

For every 10 mm rise in left atrial size the age adjusted risk of stroke double in men and women , was shown in Framingham study. Another important finding related with stroke is valvular strands.These are filamentous process attached to mitral and aortic valves . Two preliminary studies showed that these valvular strands predisposes to stroke, but more prospective studies are needed.

Patent foramen ovale and myocardial disease are also a risk factor for stroke.The risk of stroke is 0.2% to 0.3% after cardiac catheterization and angioplasty.Radiofrequency ablation, pacing,electrophysiological procedures and cardioversion , all can lead to embolic complications.

DIABETES MELLITUS: Because of increased preponderance for atherosclerosis and atherogenic risk factors like obesity , hyperlipidemia, hypertension, prospective epidemiological studies showed that the relative risk of stroke in diabetic individuals ranges from 1.8 to 3.0.In Framingham study, individuals with glucose intolerance , there is double the risk of stroke in diabetic patients when compared to non-diabetics.Hyperinsulinemia and increased insulin resistance causes diabetes to play a major role as risk factor for stroke.

LIPIDS: There is a positive correlation between LDL and total cholesterol and incidence of stroke[19], and protective role of HDL

cholesterol in extracranial atherosclerosis. Asymptomatic carotid artery plaque study showed fewer strokes in lovastatin versus placebo group.

SMOKING: There is clear dose response relation between smoking and stroke.The relative risk (RR) of smoking in causing stroke is 2.In Framingham study there is a prompt reduction in stroke risk after cessation of smoking.

ALCOHOL: A J – shaped association curve was established in a overview analysis of stroke studies, for the relation of moderate consumption of alcohol and ischemic stroke. There is increased risk for brain hemorrhage with increasing alcohol consumption.

DRUG ABUSE: The drugs that are linked to stroke are amphetamines, heroin, LSD,PCP and marijuana

ORAL CONTRACEPTIVES: There is a high risk for stroke with oral contraceptives containing estrogen content > 50micrograms.However low dose estrogens disclosed no increased risk of stroke.[22]

HOMOCYSTEINE: There is a strong relation of homocysteine levels to stroke shown recently in British Regional Heart Study, among middle aged men.There is a high level of biological plausibility that high levels of homocysteine are both prothrombotic and atherogenic[21].Vitamin

B6, B12, Folic acid though reduces the homocysteine levels , there is less evidences to prove that this intervention will reduce the incidence of stroke.

SEDENTERY LIFE STYLE: There are evidences to support the fact that moderate physical activity reduces the incidence of stroke. It exerts a protective effect against atherosclerotic disease by reducing weight, blood pressure**23** , pulse rate, lowering LDL, raising HDL, increasing insulin sensitivity and decreasing platelet aggregability

Obesity is associated with high levels of glucose, blood pressure and atherogenic lipids in serum which are serious risk factors to stroke incidence. In men aged 35-64 years and women aged 65 – 94 years , obesity which is defined as Metropolitan Life chart relative weight more than 39% above average is a significant contributor to incidence of stroke , shown in Framingham study.

Food habits like increased consumption of fish, milk, green tea are protective against stroke. Diets which are rich in fats and cholesterol are deleterious.

MIGRAINE: There is a good association between stroke and migraine[23.] The presence of migraine increased the stroke incidence from 10 in 1 lakh woman-years to 19 in 1 lakh woman-years.However the magnitude of the risk of stroke associated with migraine is small.

ASYMPTOMATIC CAROTID STENOSIS: On routine screening, presence of carotid bruit indicates the presence of stenosis of carotid artery.The rate of stroke is 1% to 2%annualy in persons who are diagnosed with cervical bruit which is asymptomatic.With progressing and more severe bruit , the risk of stroke also increases.

Risk factors increase the probability of stroke independently, however they also can interact with each other to increase the risk of stroke.

CAUSES OF ISCHEMIC STROKE:

COMMON CAUSES:

THROMBOSIS:

Large vessel thrombosis

Lacunar stroke

Dehydration

EMBOLIC OCCLUSION:

ARTERY TO ARTERY OCCLUSION

Carotid bifurcation

Arterial dissection

Aortic arch

CARDIO EMBOLIC

Atrial fibrillation

Mural thrombus

Myocardial Infarction

Dilated cardiomyopathy

Valvular lesions

Mitral stenosis

Mechanical valve

Bacterial endocarditis

Paradoxical embolus

Atrial septal defect

Patent Foramen ovale

Atrial septal aneurysm

Spontaneous echo contrast

UNCOMMON CAUSES:

Hypercoagulable Disorders

Protein C and S deficiency

Antithrombin III deficiency

Antiphospholipid antibody syndrome

Factor V leiden mutation

Prothrombin G20210 mutation

Systemic malignancy

Sickle cell anaemia

Beta thalassemia

Polycythemia vera

Homocysteinemia

DIVC

- Nephrotic syndrome
- Systemic lupus erythematosus

Venous sinus thrombosis

Fibromuscular dysplasia

Vasculitis

Drugs

- Cocaine
- Amphetamine

Cardiogenic

- Mitral valve calcification
- Atrial myxoma

Moya moya disease

Eclampsia

STROKE PATHOPHYSIOLOGY

Ischemia and hemorrhage are the two most important mechanism in stroke that causes the brain damage. However 80% of the stroke are ischemic stroke, in which there is absent or reduced blood flow which deprives the necessary substrates to the neurons.Because the brain does not store the chief substrate of energy , glucose , and is incapable of anaerobic metabolism,hence ischemia ensues fair rapidly.

FOCAL ISCHEMIC INJURY. A cerebral artery can be occluded either by a thrombus or embolus and creates ischemia in the vascular territory.There is difficulty in distinguishing a lesion which is caused by thrombus and the one caused by embolus.The extent of ischemic injury and its progression are influenced by many factors.

RATE OF ONSET AND DURATION: The brain tolerates an ischemic event of slow onset and of short duration.

COLLATERAL CIRCULATION: There is better outcome associated with collateral circulation

BLOOD PRESSURE: Adequate systemic blood pressure is needed to maintain constant cerebral perfusion pressure. Systemic hypotension can result in global cerebral ischemia.

TEMPERATURE: Greater cerebral injury is associated with elevated body temperature.

HEMATOLOGICAL FACTORS: The progression and extent of microscopic thrombi exacerbated by hypercoagulable state.

GLUCOSE METABOLISM: The size of an infarct is adversely influenced by hypo- hyperglycemia[25-27]

CEREBRAL BLOOD FLOW: Normal cerebral blood flow is 50 to 60 ml/100g/min.Cerebral autoregulatory mechanisms causes local vasodilation whenever there is reduction in cerebral blood flow(CBF).

When the cerebral blood flow is reduced below 20ml/100g/min, the synaptic activity is reduced to preserve the energy stores.There is irreversible neuronal injury when the cerebral blood flow is less than 10ml/100g/min.

MECHANISM UNDERLYING NEURONAL INJURY: Ischemia induces the release of destructive vasoactive enzymes by platelets, leucocytes, endothelium and other neuronal cells,results in formation of a microthrombi.This microthrombi is responsible for impairment of circulation in capillaries and cerebral arterioles.

The “overreaction” of certain neurotransmitters glutamate[28-32] and aspartate causes the development of hypoxic ischemic neuronal injury.Depletion of cellular energy stores causes triggering of this process called “excitotoxicity”. Glutamate is normally present inside the synaptic terminals.It is cleared by energy dependent process from the extracellular space.In energy depleted state, the glutamate accumulates in the extracellular space results in opening of the calcium channels.This calcium channel is associated with N-methyl-D-aspartate(NMDA) and alpha-amino-3-hydroxy-5-methyl-4 isoxanolepropionate (AMPA) receptors. There is influx of calcium, chloride, sodium ions and potassium efflux due to persistent membrane depolarisation.

There is series of destructive enzymes activation such as proteases , endonucleases and lipases by intracellular calcium. This causes release of cytokines resulting in loss of cellular integrity.

As early as 30 minutes after the event of ischemia and reperfusion,there is leukocyte recruitment to the ischemic area.

The leukocyte causes the activation of vasoactive substances like arachidonic acid metabolites and oxygen free radicals.These causes

Vasoconstriction,

increased permeability,

increased adherence of leukocyte to the endothelial wall,

increased platelet aggregation and

immunoregulation.

ENDOTHELIAL CELL RESPONSE: Endothelial cell is the first cell to respond to hypoxia.It swells up and forms a ‘microvilli’ at the luminal side of the cell.This causes decreased luminal patency of the capillary vessel, resulting in mechanical plugging by the leukocytes,erythrocytes and platelets.

The vascular tone of the microcirculation is modulated by the endothelin peptides, NO, eicosanoids which are mediated by the endothelial cells. The endothelial adhesion molecules when they are activated promotes the adherence of the leukocyte to the endothelial wall, which plays a major role in the activation of the inflammation process.

ISCHEMIC PENUMBRA:

Ischemic penumbra[34,35] is a zone of oligaemia which surrounds the core of infarction within an hour of hypoxic-ischemic insult, where autoregulation is ineffective. “ Window of opportunity” is the critical time period,during which this volume of brain tissue is vulnerable. Because the ischemia which causes the neurological effects can be

completely or partially reversed by reperfusing the ischemic but viable brain tissue within critical period of time(2-4 hours)

The cerebral blood flow is 25% to 50% of normal in the ischemic penumbra(IP), hence there is preservation of some energy metabolism. For variable period of time the integrity of cells and its function is preserved in this ischemic penumbra. Generation of spontaneous waves of depolarisation(SWD) is closely linked to the pathophysiology of IP. This spontaneous waves of depolarisation originates from ischemic core and also from ischemic foci of periinfarct zone.

The development of spontaneous waves of depolarisation is also linked to sustained release of glutamate and extracellular potassium.This spontaneous waves of depolarisation can be suppressed by the glutamate receptor antagonists.

Before irreversible neuronal death ,rapid or hypoxic depolarisation supervenes eventually.

NEURONAL DEATH:

The injured neurons die by two process, namely,

1. Coagulation necrosis

2. Apoptosis

COAGULATION NECROSIS:

Coagulation necrosis(CN) is a process in which the cell die without eliciting an inflammatory response among the living neighbour cells. Effects of chemical, physical or osmotic damage to the plasma membrane is linked to this type of cell death.This occurs as in contrast to the liquefaction necrosis where the space which is left behind by the dying cells which is filled by pus due to inflammatory process.

In coagulative necrosis, the cell swells initially then shrinks , finally undergoes nuclear chromatin condensation called “pyknosis”.Over six to twelve hours this process evolves.Pan necrosis occurs due to extensive chromatolysis by 24 hours.Astrocyte swell and fragments.Then occurs degeneration of myelin sheath. Between 8-12 hours after the occlusion of the artery, there occurs irreversible cell injury as evidenced by eosinophilic cytoplasm and shrunken nuclei.

APOPTOSIS:

Cerebral neurons are programmed to die in conditions like ischemia. Nuclear damage occurs first during apoptosis. Until late in the process the integrity of the plasma membrane and mitochondrial membrane is maintained. Autolytic process is started by the latent suicide proteins triggered by the ischemia, causing death of the cells. DNA cleavage mediates this autolytic process.

After 1 hour of ischemic injury the apoptotic mechanisms occurs as contrast to coagulative necrosis which begin after 6 hours. Hypothetically, by modifying the process of DNA cleavage, neuronal death can be prevented.

ISCHEMIC STROKE:

Ischemic stroke is caused by three major mechanisms

1. Thrombosis
2. Embolism
3. Global ischemia

However not all ischemic stroke fall into these categories

THROMBOSIS:

The most important pathological feature of vascular obstruction is atherosclerosis. Atherosclerotic plaque can undergo pathological changes like

a) Ulcerations,

b) Thrombosis,

c) Calcification and

d) Intra plaque hemorrhage

The structure, consistency and composition of the plaque decides the susceptibility of the plaque to ulcerate, disrupt and fracture. This causes disruption of endothelium activating many vasoactive enzymes.Then follows the platelets adherence and aggregation forming platelets and fibrin nidi.Within 1 hours the leukocytes initiates the inflammatory process.

Apart from atherosclerosis other conditions that causes thrombotic occlusion are,

Hypercoagulable state,

Fibromuscular dysplasia,

Arteritis and

Dissection of vessel wall

Lacunar infarcts[36,37] ,occur as a result of deep penetrating artery occlusion . As a result of long standing hypertension and diabetes mellitus the small arteriole becomes tortuous and subintimal dissections and microaneurysms develops.This makes the arteriole susceptible to occlusion from micro thrombi. The underlying pathological mechanisms is ‘lipohyalinosis due to fibrin deposition’.

EMBOLISM:

Embolic stroke occurs as a result of embolisation from a variety of sources of an artery of central circulation. Materials that can embolize are atheromatous plaque pieces,fibrin, clot,air,fat,tumor or metastases,foreign bodies, bacterial clumps. The most frequent targets are the superficial branches of superior cerebellar and cerebral arteries. As nearly 80 % of the blood carried by the large neck arteries flow in the middle cerebral artery,most of the emboli lodge in the distribution of middle cerebral artery.

CARDIO EMBOLIC STROKE:

20% of all ischemic stroke is due to cardio embolism.The thrombotic material attached to the atria, left ventricle or the valves detach and embolize into the circulation.The thrombi may only lyse or fragment so quickly to produce a TIA.If the occlusion lasts longer it

produces stroke.Embolic stroke is of sudden onset with maximum neurological deficit at the time of presentation. With reperfusion petechial hemorrhage tend to occur at the site of ischemic territory.However it is of no neurological significance and it must be distinguished from hemorrhage into the ischemic area, which can produce mass effect and cause decline in the neurological function

The order of involvement of vessels due to embolism from the heart are, Middle cerebral artery, posterior cerebral artery or its branches, and infrequently anterior cerebral artery. The most important causes of cadioembolism are nonrheumatic atrial fibrillation, myocardial infarction (MI), rheumatic heart disease(RHD),and ischemic cardiomyopathy.

Paradoxical embolisation occurs when a venous thrombi migrate via patent foramen ovale or ASD into the arterial circulation. Even fat, air, amniotic fluid, bacterial endocarditis an be responsible for paradoxical embolization other than venous clot. Bacterial vegetations can give rise to septic emboli. In a stroke patient with multifocal signs and symptoms more likely is the presence of bacterial endocarditis.

ARTERY TO ARTERY EMBOLIC STROKE:

A thrombus can form over an atherosclerotic plaque which can embolise into intra cranial artery ,causing artery to artery embolic stroke. Most common source of artery to artery embolic stroke is the atherosclerosis of carotid bifurcation. The dominant mechanism of brain ischemia is artery to artery embolism rather than local thrombosis unlike in myocardial vessels.

Other causes of artery to artery embolic stroke are intracranial atherosclerosis and dissection of internal carotid or vertebral arteries or even the vessels beyond the circle of willis.

The outcome of the embolic stroke depends on the ability of the embolus to initiate vasospasm by acting as vascular irritant. It tends to occur more commonly in young patients because of the more pliable and less atherosclerotic vessels.

When a bleeding develops in the necrotic cerebral tissue it is called as hemorrhagic transformation of an ischemic infarct.When a embolus is lysed spontaneously and restoration of blood flow occurs causing reperfusion, hemorrhagic transformation ensues. In the presence of persistent arterial occlusion, reperfusion can occur from collateral circulation from leptomeningeal vessels.

The major factors associated with the hemorrhagic infarcts are the

1. Size of the infarct
2. Collateral circulation
3. Use of anticoagulants
4. Interventional therapy with thrombolytic agents

GLOBAL – ISCHEMIC OR HYPOTENSIVE STROKE:

Hypotensive stroke occurs due to profoundly reduced systemic blood pressure due to any cause.The viable neurons are

1. Pyramidal cell layer of the hippocampus,
2. Purkinje cell layer of the cerebellar cortex and
3. Cerebral gray matter

It is the more abundant glutamate in these neurons which makes them more vulnerable to global ischemia. The greatest damage also occurs to the “water shed areas” or the “boundary zone” formed by the territories of the cerebellar and cerebral arteries. The most commonly affected area is the parieto-temporo-occipital triangle ,which is formed at the junction of anterior,posterior and middle cerebral arteries.

Water shed infarction of this area causes a clinical syndrome which consists of sensory loss and paralysis of arm but speech and face are

spared. Nearly 10 % of all the ischemic strokes are water shed infarcts and 40% of the watershed infarct occurs due to carotid occlusion or stenosis.

STROKE SYNDROMES

The clinical picture that occurs from an occlusion of any one artery differs in some ways from one patient to the other.However there is enough uniformity to justify the establishment of a certain syndrome to each of the major cerebral arteries and their branches.Their identification by meticulous examination of specific neurovascular syndromes is the cardinal skill of the clinical neurologist. The following descriptions can be applied especially to the clinical effects of infarction produced by embolism and thrombosis.

CAROTID ARTERY NEOVASCULAR SYNDROME:

The carotid system has three major arteries:

the common carotid artery

internal carotid artery

external carotid artery

Occlusion of the common carotid artery accounts for nearly less than 1 percent of cases . The remainder of the cases are because of disease of the internal carotid artery . However the common carotid can be occluded by an atheromatous plaque at the origin, mostly on the left side. Atherosclerotic stenosis of the middle part of the common carotid also occur many years after radiation therapy for thyroid, laryngeal or other head and neck cancer.

If the bifurcation is patent, only few symptoms ensue because of the retrograde flow from the external carotid which maintains the internal carotid artery flow and hence the perfusion of the brain.

In most of the individuals the internal carotid artery is in continuity with the circle of Willis and with the vessels of the orbit, and no part of the brain is entirely dependent on it. Therefore the occlusion, that occurs mostly in the first part of the internal carotid artery immediately beyond the carotid bifurcation, will be usually silent in about 30 to 40 percent of cases.

If one internal carotid artery was occluded before, occlusion of the other internal carotid artery may cause bilateral cerebral infarction. The clinical effects in such cases are coma with quadriplegia and also horizontal "metronomic" conjugate eye movements which is continuous.

When the circulation of one internal carotid artery is compromised incompletely, reducing blood flow in middle and anterior cerebral arterial territories on ipsilaterally, then the zone of ischemia which is maximal lies between the two vascular territories ("cortical watershed") or lies in the deeper portions of the cerebral hemisphere between the territories of the penetrating vessels from the convexity and the lenticostriate branches ("internal" or "deep watershed").

The infarction of the first instance lies at a region in the high frontal and parietal cortex and the subcortical white matter.The size of the infarct depends upon the adequacy of the collateral circulation. Clinically more weakness is found in the shoulder and hip than the face and hand. If the carotid stenosis is long standing, then the cortical watershed area shifts toward the perisylvian portions of the middle cerebral territory, to the extent that a stroke may cause weakness of facial movement or cause nonfluent aphasia. Infarctions of different size are situated in the subparietal and subfrontal portions of the centrum semiovale with impaired perfusion of the deep watershed area.

ANTERIOR CEREBRAL ARTERY STROKE SYNDROME:

Anterior cerebral artery through the cortical branches, supplies,

1. the medial surface of the frontal lobe in its anterior three quarters,
2. the frontal pole,
3. medial-orbital surface of the frontal lobe,
4. a strip of the cerebral hemisphere in its lateral surface along with the superior border , and
5. anterior four-fifths of the corpus callosum.

Deep branches, which arise near the circle of Willis supply the anterior limb of the internal capsule,

1 .The anterior part of the globus pallidus

2. The inferior part of the head of the caudate nucleus

Occlusion of the anterior cerebral artery stem, proximal to the connection of anterior communicating artery is tolerated well, as there is adequate collateral flow which is provided by the opposite side anterior cerebral artery

Occlusion distal to the anterior communicating artery causes a sensorimotor deficit of the foot and leg in the opposite side and, also of the arm and shoulder, with sparing of the face and hand.

A contralateral grasp reflex, urinary incontinence and paratonic rigidity of the opposite limbs will be seen. There may be "sympathetic apraxia" of the left arm and leg with left sided occlusion. Language disturbances, like transcortical motor aphasia may occur .

MIDDLE CEREBRAL ARTERY STROKE SYNDROMES:

The middle cerebral artery (MCA) supplies the major part of the cerebral hemisphere through its superficial and deep hemispheral branches. The lateral (convexity) part of the cerebral hemisphere is supplied by its cortical branches which encompasses.

(1) the cortex and white matter of the inferior and lateral parts of the frontal lobe—which includes motor areas 4 and 6, the motor speech area of Broca and the contraversive centers for lateral gaze.

(2) the cortex and white matter of the parietal lobe, which includes angular and supramarginal gyri, the primary and secondary sensory cortices.

(3) the superior parts of the insula and temporal lobe, which also includes the receptive language area of Wernicke.

The lenticulostriate branches of the MCA supply large part of the head and body of the caudate nucleus, the putamen, the posterior limb of the internal capsule, outer globus pallidus and the corona radiate.

MCA STEM OCCLUSION:

The MCA may be occluded at the stem, which is proximal to the bifurcation .An occlusion at this site blocks the blood flow in the superficial cortical branches and small deep penetrating vessel.However the orifices of the divisions of the artery at the sylvian sulcus is affected if the occlusion occurs at the distal end of the stem of the MCA and leaves the deep penetrating vessels unaffected.

The clinical picture includes contralateral hemiplegia , homonymous hemianopia and hemianaesthesia with head and eyes deviated toward the side of the lesion. There is also anosognosia and amorphosynthesis with lesions of the right side and global aphasia with left sided lesions.

SUPERIOR DIVISION:

Infarction in the region of the superior division causes a motor weakness and sensory loss in the contralateral arm, face, also to some extent the leg, and also ipsilateral deviation of head and eyes.It mimics the syndrome of MCA stem occlusion but the leg and foot are partly spared and if involved the weakness is less when compared to the face and arm("brachiofacial," or chierobrachial paralysis).But the alertness is preserved.

If the occlusion is long-lasting there will be a very slow improvement. After a few months, the motor deficits of the arm and face remain and the patient will be able to walk with a spastic leg. The sensory deficit will be profound, resembles a thalamic infarct and it is less severe when compared with the motor deficit, which takes the form of stereoanesthesia, impaired tactile localisation, impaired position sense, agraphesthesia, and impaired two-point discrimination, and also variable changes in pain,touch and temperature sense.

With left-sided lesions there is a global aphasia initially, which then changes to a predominantly nonfluent aphasia, or a Broca's aphasia from the outset.

INFERIOR DIVISION:

Occlusion of the inferior division of the MCA is less frequent than the occlusion of the superior division, and is usually due to embolism. The clinical feature in left-sided lesions is a Wernicke's aphasia, and remains static for days or weeks after that period some improvement can be expected.

In selective distal branch occlusions (superior parietal,posterior temporal,angular), there is a severe deficit in comprehension of written and spoken language. After a few months, the deficits improves.

With left-hemispheric lesions, there is a homonymous hemianopia or superior quadrantonopia .With right-sided ones, a left visual neglect and signs of amorphosynthesis. Rarely, an agitated confusional state, due to a damage from temporal lobe, may be a presenting feature of dominant hemispheral lesions and even of nondominant ones.

POSTERIOR CEREBRAL ARTERY STROKE SYNDROME:

In about 70 percent of individuals, both the posterior cerebral arteries are formed by the basilar artery bifurcation and thin posterior communicating arteries join the above system to the internal carotid arteries. In approximately 20 to 25 percent of the indiividuals, one posterior cerebral artery arises from the basilar , and the other arises from

the internal carotid artery, a persistent fetal circulation pattern.However in less than 5 percent of the individuals there is an unusual pattern in which both the posterior cerebral artery arise from the corresponding carotid arteries.

Since the upper brainstem, which has most important structures, and also the occipital lobe and the inferomedial parts of the temporal lobes lie within the supply of the posterior cerebral artery, occlusion of this artery produces more variety of clinical effects than any others. The circle of Willis arrangement and the occlusion site will in greater measure determine the extent and location of the resulting infarct.For instance, occlusion which is proximal to the posterior communicating artery may be asymptomatic , or otherwise it can have only clinical effects which is very transient due to the collateral flow which is adequate from the opposite posterior cerebral vessel. Also an occlusion which is distal to the posterior communicating artery may cause less damage if the border-zone collaterals from anterior and middle cerebral arteries are sufficient.

CORTISOL AND STROKE:

There is an early and massive activation of Hypothalamo-Pituitary-Adrenal axis(HPA) seen in hyperacute phase of stroke. Biphasic pattern of response is observed characteristically. ACTH and cortisol are increased concomitantly initially.In second phase, cortisol levels remains increased though there is a rapid decrease of ACTH levels.

The above mentioned pattern is explained by the fact that the initial activation of HPA axis is soon followed by very stong cortisol induced suppression of levels of ACTH.Also the increased susceptibility of the adrenal gland maintains the elevated cortisol levels.Surprisingly the adrenal gland hyperresponsiveness to ACTH is also shown in the early recovery state of postoperative state.

The proinflammatory cytokines that are released in tissue injury possess a ACTH or corticotrophin releasing hormone(CRH) like activity which explains the strong response of adrenal gland in the absence of increase of ACTH parallelly and its relation to the extent of brain damage.

The concept of neurotoxicity of the HPA hormones is established in many in vivo and invitro strudies.It clearly outlines that the cortisol causes damage to the brain by

1. exacerbating the hypoxic injury to astrocytes and the neurons[38-40], and by

2. Impeding glucose uptake and its metabolism in the brain

Higher cortisol levels is linked to cognitive dysfunction due to the fact that hypercortisolism can cause reinforcement of ischemic damage to the hippocampal neurons[41-43,50].Also it is linked with higher morbidity and poorer functional outcome in stroke patients[44,45].

Also it is found that repeated stresses are common to the patients with acute ischemic stroke in the form of infections ,emotional reactions, and cardiovascular complications.The adrenal sensitivity to ACTH can be increased by repeated stresses. And hence hypercortisolism can be prolonged.

ROLE CYTOKINES IN CORTISOL AXIS ABNORMALITIES AFTER STROKE:

Proinflammatory cytokines[9,10] are release in a cascade after the brain infarction.It is the TNF alpha which starts the cascade after ischemia, which in turn activates interleukin 1 and 6. Sympathetic nervous system activation also contributes to the effect.

There are multiple levels at which interleukin – 6[47-49] can be regulated in acute ischemic stroke. Also any psychological and physical stressors can elevate the interleukin – 6 levels because of the activation of hypothalamo pituitary adrenal axis. After the event of acute stroke many inflammatory cytokines are released from the peripheral blood cells.

There is also a finding that abnormal leptin[11] levels with flattening of diurnal variations in patients with stroke.There are more evidence that leptin[46] is associated with neuroendocrine balance which also includes cortisol axis regulation.There are studies which shows that initial IL-6 levels and abnormal diurnal rhythmicity of cortisol levels can predict stroke outcome.

MATERIALS AND METHODS

STUDY DESIGN

STUDY GROUP	:	All new cases of acute ischemic stroke admitted in KMCH within 72 hours of acute neurological event satisfying the inclusion and exclusion criteria
TYPE OF STUDY	:	Cross Sectional Study Stratified across Severity Scales
SAMPLE SIZE	:	50
PLACE OF STUDY	:	Department of General Medicine Kilpauk Medical College Hospital
DURATION OF STUDY	:	6 Months from April 2014 to September 2014

BACKGROUND

Inclusion criteria :

1. Patients in the age group of above 18 years
2. Patients proven to have acute ischemic stroke admitted within 72hrs of onset of neurological event (by CT Brain - Plain)

Exclusion criteria :

1. Age< 18 years
2. Pregnancy
3. Liver disease
4. Patient who are taking following drugs :

   Immunosuppresants,Steroids, Rifampicin, Phenytoin.
5. H/o malignancy
6. Hemorrhagic stroke
7. Acute febrile illness
8. Major Surgery within 3 weeks

METHODOLOGY:

The data of each patient was collected in the specific proforma which included,

1. Patient name, age ,sex, demographic details,presenting complaints, risk factors, past history,drug history
2. General examination
3. Vital signs
4. System examination
5. Severity assessment by using National Institute of Health Sciences Scale(NIHSS) at the time of admission
6. Serum Cortisol levels measured on the next day early morning
7. CT Brain plain
8. Morbidity and Mortality reassessment after 15 days using Modified Rankin Scale.

Finally serum cortisol levels are compared with NIHSS score and MRS score and levels more than 690nmol/L is considered to be elevated

and severity assessed as defined by NIHSS score (score>6)at the time of admission and modified Rankin scale(scale >3) during follow up

BIOCHEMICAL ANALYSIS

Blood samples were taken on the next day morning after admission and serum cortisol levels measured.

The serum cortisol is measured quantitatively using Enzyme Immuno Assay.

PRINCIPLE OF THE TEST:

The principle of the test is based on the competition that is occurring between the unlabelled antigen and the antigen which is enzyme labelled for a limited antibody binding sites on the microwell plates.The unbound materials are removed by washing and decanting methods.The enzyme substrate is added.By the addition of stop solution enzymatic reaction is terminated.The microtitre plate reader measures the absorbance.The intensity of the formed colour is inversely proportional to the cortisol concentration in the sample.A set of standards are used to plot a standard curve. Through which the amount of cortisol is directly read.

TEST:

5 ml of venous blood is collected into the collecting tube and allowed it to clot and centrifuged and the serum layer is removed. Working solutions of the cortisol Horse Radish Peroxidase conjugate and wash buffer is prepared.The required number of microwell strips are removed in a polyclonal antibody coated microwell plate. 20microlitre of each calibrator,control and specimen sample is pipetted into the corresponding labeled wells in duplicate.100 microlitre of conjugate working solution is pipetted into each well. Then it is incubated in to a plate shaker(around 200rpm) for forty five minutes at room temperature.Then the wells are washed with diluted wash buffer and dried.150 microlitre of tertra methyl benzidine substrate is pipetted into each well at intervals of time.Then it is again incubated on a plate shaker at room temperature for 20 minutes.50 microlitre of stop solution is pipetted into the well at timed intervals. Within 20 minutes after the addition of the stop solution the plate is read on a micro well plate reader at 450nm.Results are calculated using mean optical density and calibrator curve and multiplied by a dilution factor.

DATA ANALYSIS

STATISTICAL ANALYSIS:

Mean values of the parameters are calculated by Independent sample – t test.

Correlation between serum cortisol levels and stroke scales are assessed by Chi – Square Test.

All statistical analysis are performed using SPSS (software package used for statistical analysis) package.

A p- value of less than 0.05 is considered to be statistically significant.

OBSERVATION ANALYSIS

TABLE: 1.AGE WISE DISTRIBUTION OF STROKE

AGE IN YEARS	NUMBER OF CASES	PERCENTAGE
31-40	3	6
41-50	4	8
51-60	9	18
61-70	19	38
71-80	11	22
81-90	4	8
Total	**50**	**100**

The minimum age of the patients is 31 years and the maximum age is 85 years. Among the 50 patients, 6% are in the 31-40 years, 8% are in the 41-50 years,18 % in the 51-60 years,38% in the 61-70 years, 22% in the 71-80 years,8% in the 81-90 years.

TABLE: 1.AGE WISE DISTRIBUTION OF STROKE

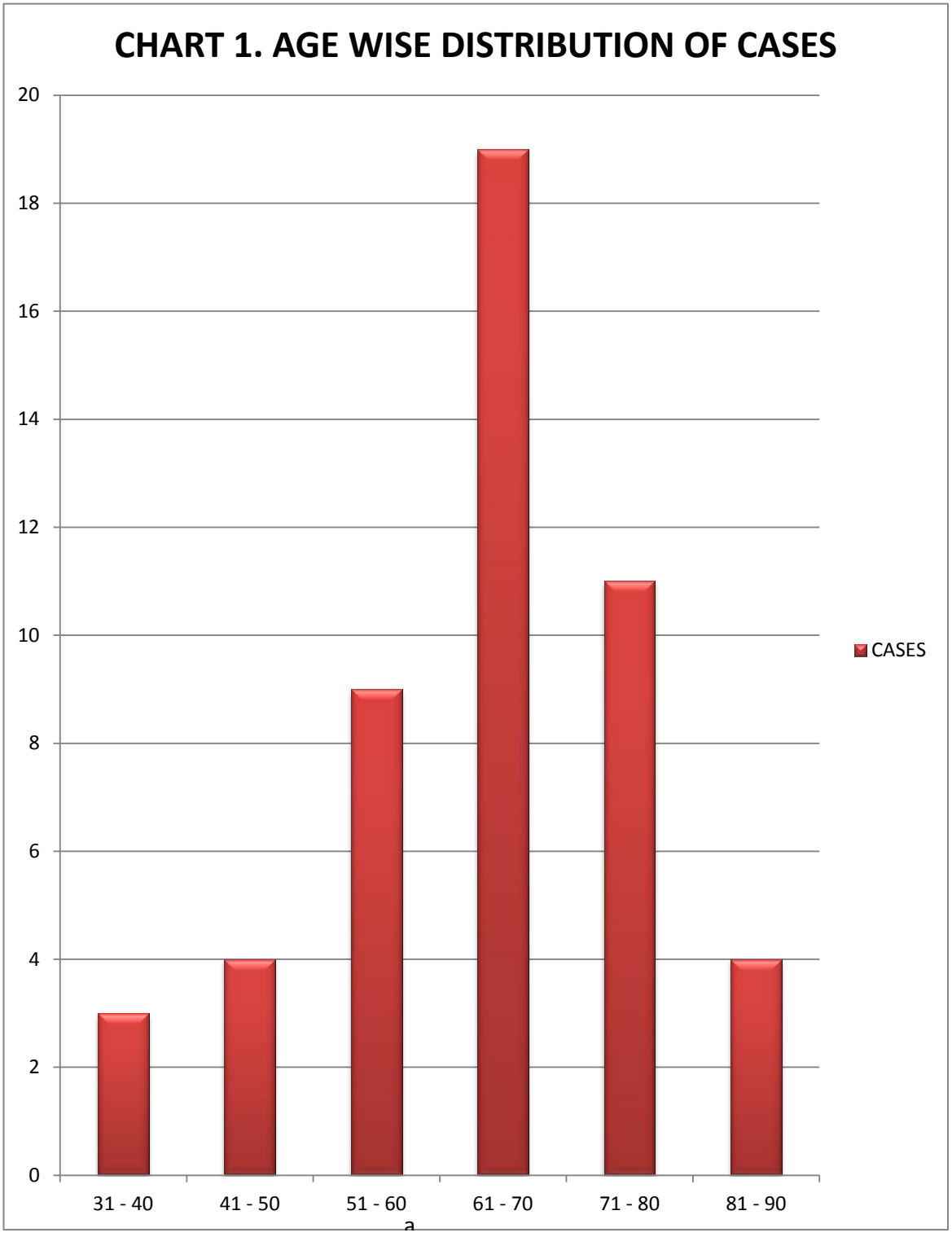


TABLE 2.SEX WISE DISTRIBUTION OF CASES

SEX	NO. OF CASES	PERCENTAGE
MALE	29	58
FEMALE	21	42

Of the 50 cases , 29 were males and 21 were female i.e.,58 percent were males and 42 percent were females

CHART 2. SEX WISE DISTRIBUTION OF CASES

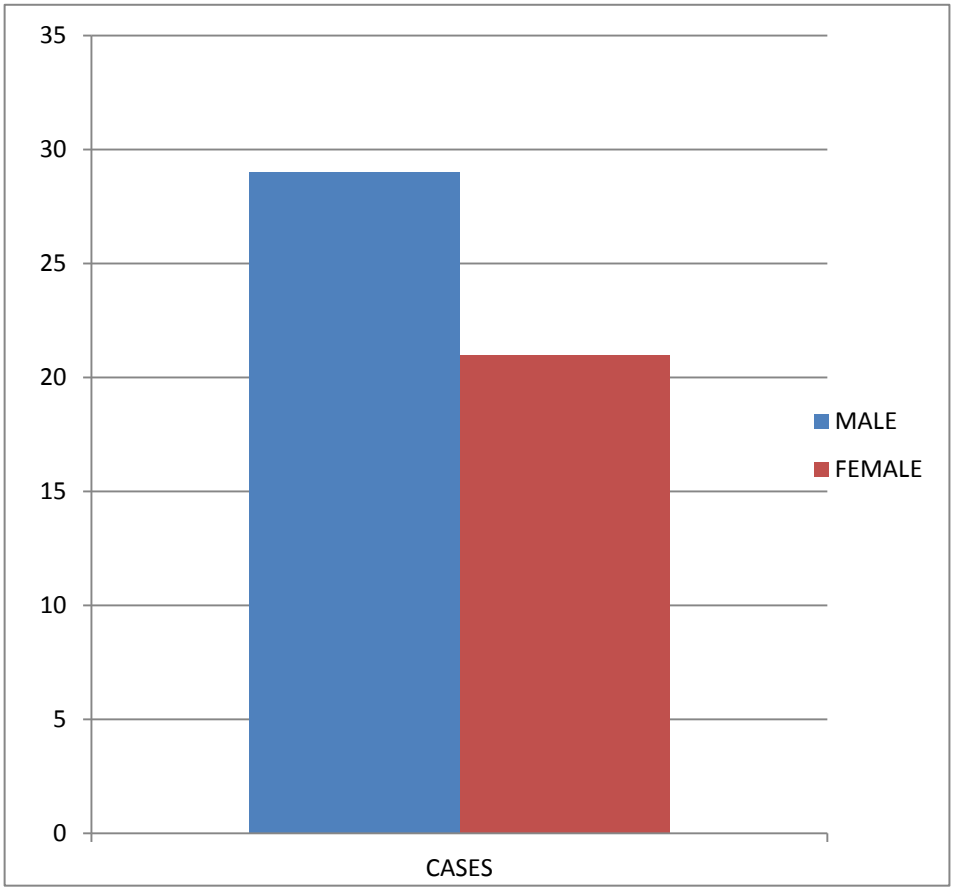


TABLE : 3 . MEAN CORTISOL LEVEL IN MALE AND FEMALE CASES

SEX	N	MEAN CORTISOL	STANDARD DEVIATION	STANDARD ERROR OF MEAN
MALE	29	631.07	138.199	25.663
FEMALE	21	659.14	194.324	42.405

Mean cortisol level in male cases are 631.07 and in female cases are 659.14.

CHART : 3. MEAN CORTISOL LEVEL IN MALE AND FEMALE CASES

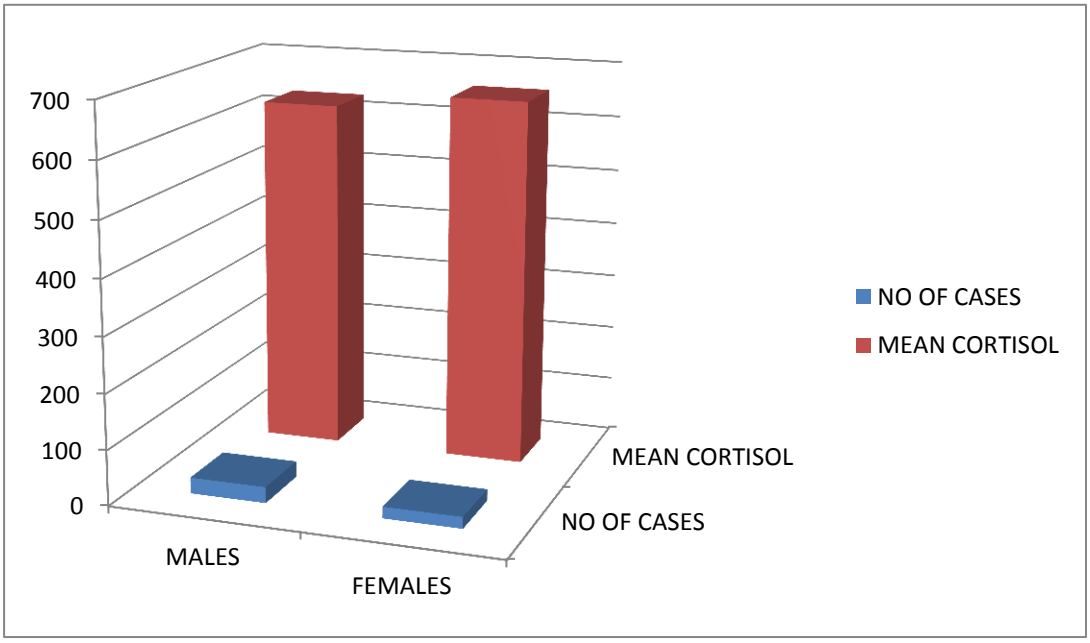


TABLE : 4. NUMBER OF DIABETICS AND NON DIABETICS AMONG CASES

	NUMBER OF CASES	**PERCENTAGE**
DIABETICS	13	26.0
NON- DIABETICS	37	74.0
TOTAL	**50**	**100.0**

Among the 50 cases, 13 were diabetics and 37 were non diabetics. i.e., 26% were diabetics and 74% were non diabetics

CHART: 4. NUMBER OF DIABETICS AND NON DIABETICS AMONG CASES

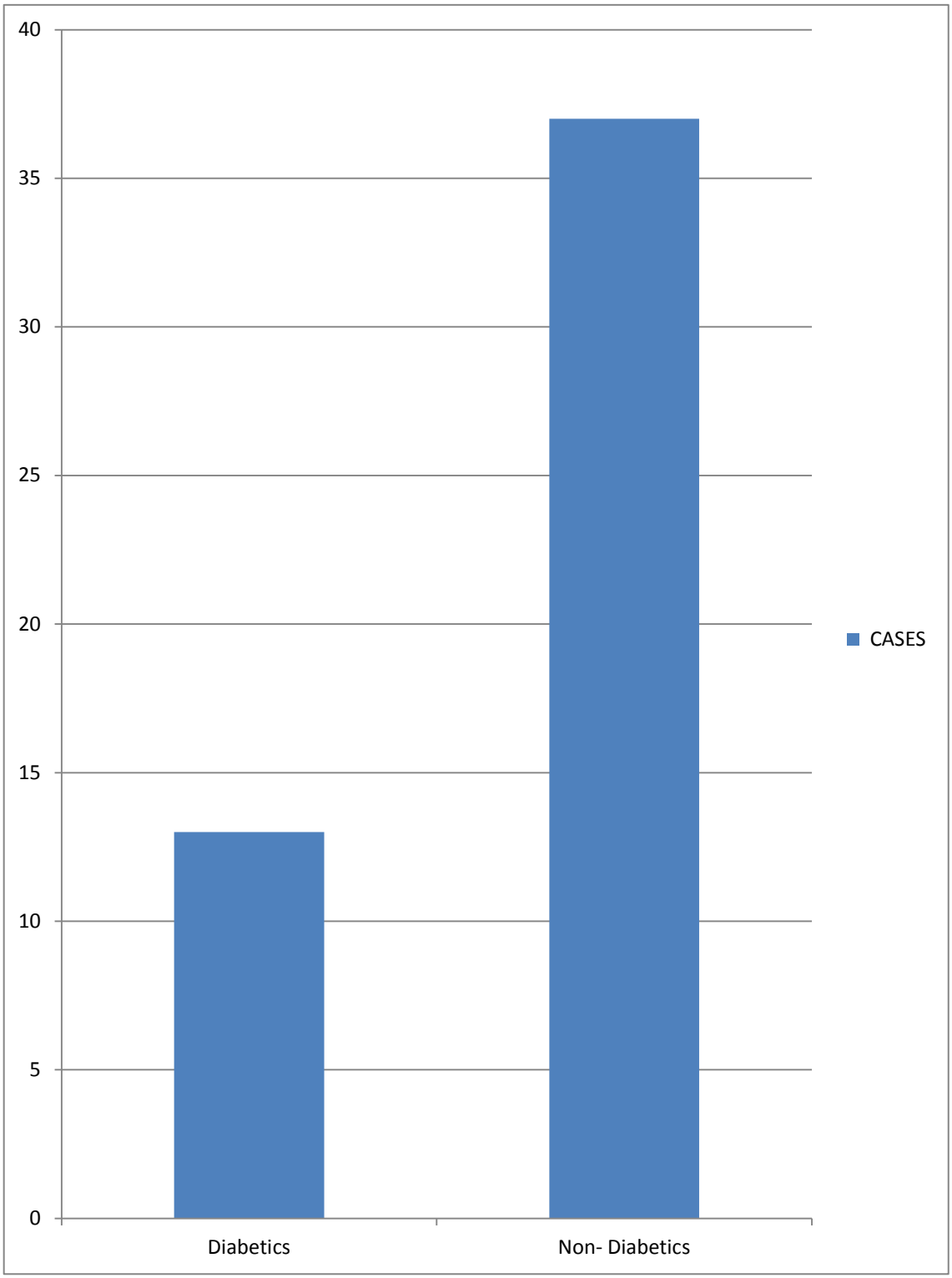


TABLE : 5. MEAN CORTSIOL LEVELS IN DIABETIC AND NON DIABETIC CASES

DIABETES	N	MEAN CORTISOL	STANDARD. DEVIATION	STANDARD. ERROR OF MEAN
YES	13	590.15	193.461	53.657
NO	37	661.38	149.227	24.533

Mean cortisol levels in diabetic cases are 590.15 and non diabetic cases are 661.38

CHART : 5. MEAN CORTSIOL LEVELS IN DIABETIC AND NON DIABETIC CASES

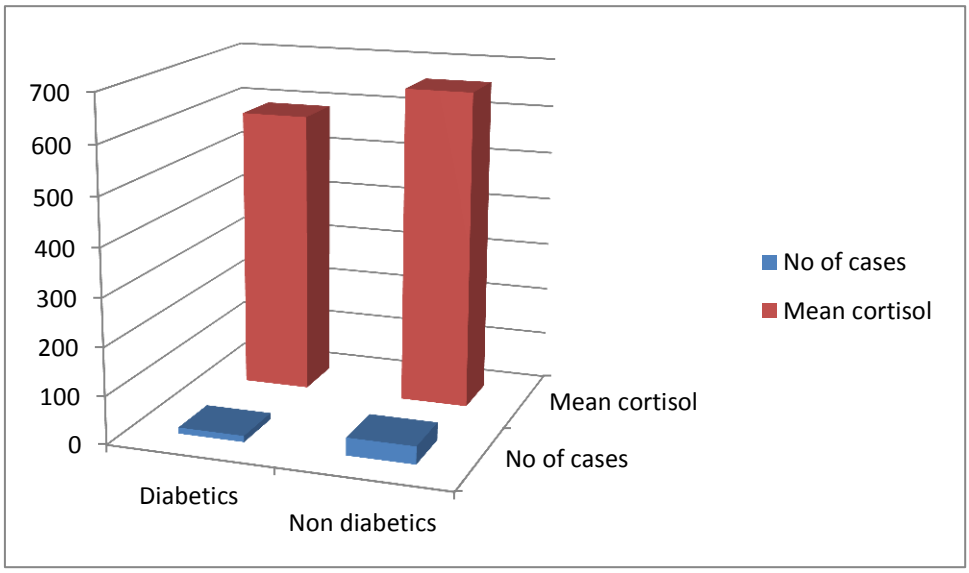


TABLE: 6. NUMBER OF HYPERTENSIVES AND NORMOTENSIVES AMONG CASES

	NUMBER OF CASES	**PERCENTAGE**
HYPERTENSIVES	20	40.0
NORMO TENSIVES	30	60.0
TOTAL	**50**	**100.0**

Among the 50 cases , 20 were Hypertensives and 30 were Normotensives . ie., 40 percent were hypertensives and 60 percent were normotensives

CHART : 6. NUMBER OF HYPERTENSIVES AND NORMOTENSIVES AMONG CASES

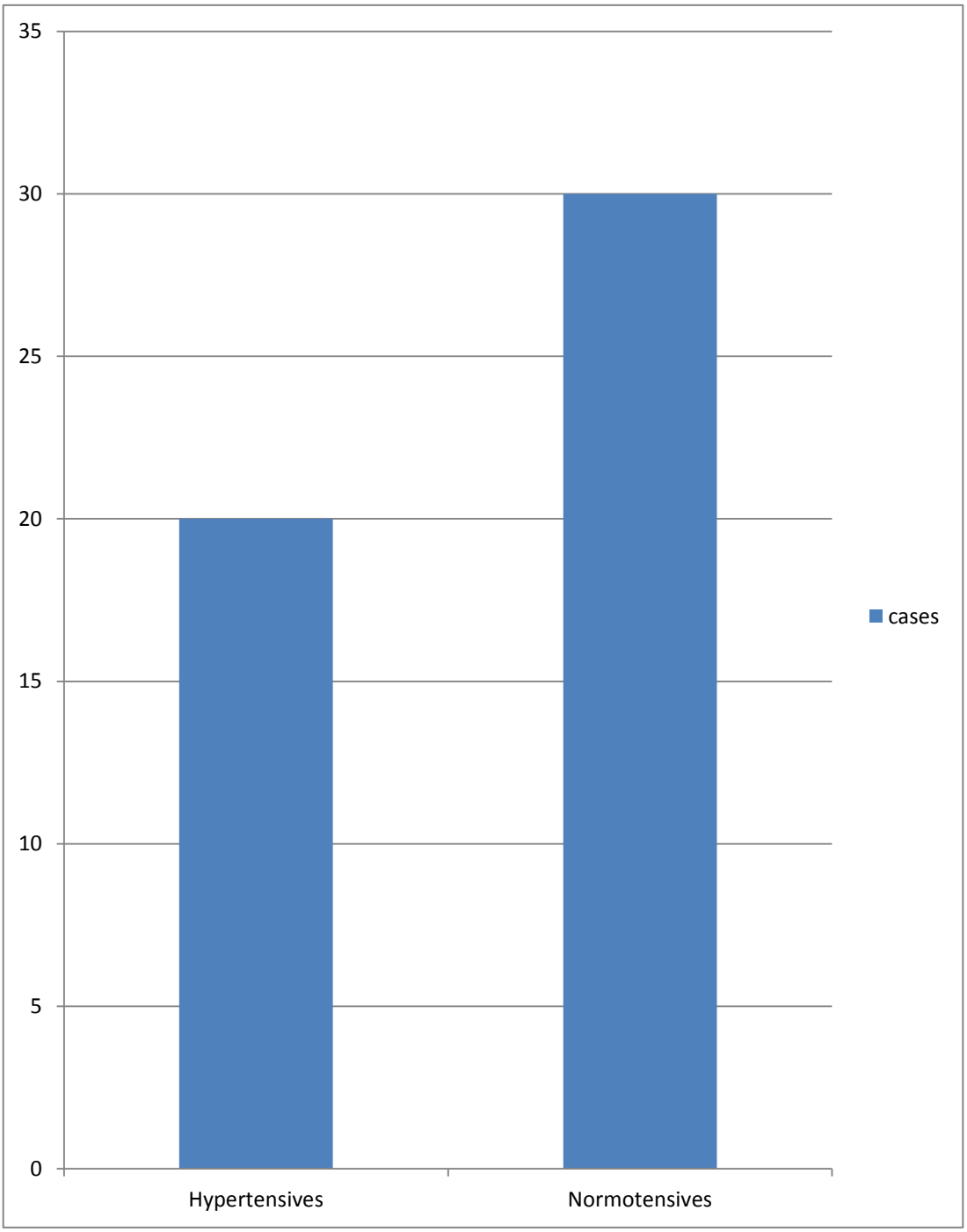


TABLE : 7. MEAN CORTISOL LEVEL IN HYPERTENSIVE AND NORMOTENSIVE CASES

HYPERTENSION	N	MEAN CORTISOL	STANDARD. DEVIATION	STANDARD ERROR OF MEAN
YES	20	657.75	174.853	39.098
NO	30	632.93	156.614	28.594

Mean cortisol level in hypertensive cases are 657.75 and normotensive cases are 632.93

CHART : 7. MEAN CORTISOL LEVEL IN HYPERTENSIVE AND NORMOTENSIVE CASES

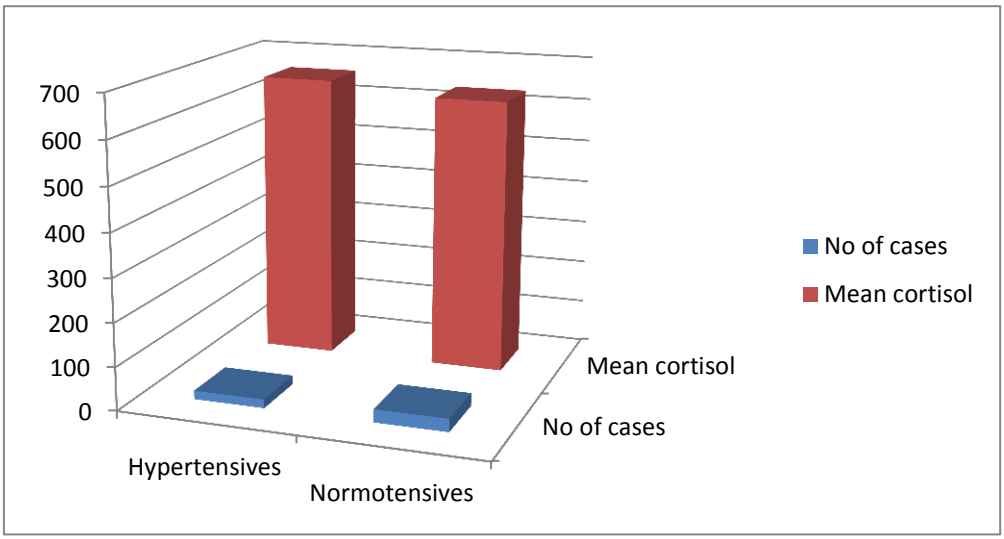


TABLE : 8. NUMBER OF CASES WITH AND WITHOUT CORONARY ARTERY DISEASE

	NUMBER OF CASES	PERCENTAGE
CAD	12	24
NON-CAD	38	76
TOTAL	50	100.0

Of the 50 cases , coronary artery disease was present in 12 and absent in 38.ie., 24 percent had CAD and 76 percent did not have CAD

CHART : 8 . NUMBER OF CASES WITH AND WITHOUT CORONARY ARTERY DISEASE

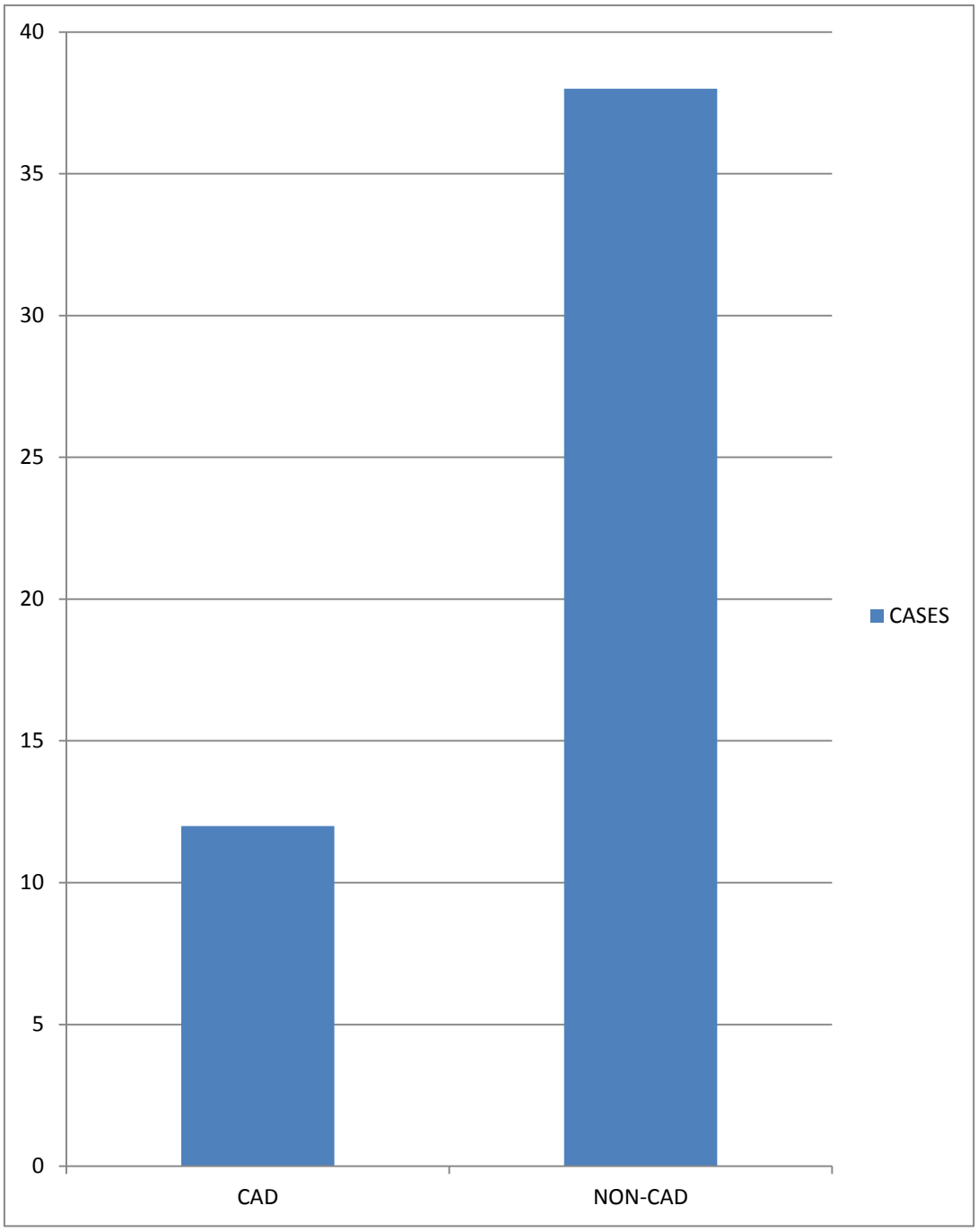


TABLE : 9. MEAN CORTISOL LEVEL IN CASES WITH AND WITHOUT CORONARY ARTERY DISEASE

CAD	N	MEAN CORTISOL	STANDARD. DEVIATION	STANDARD ERROR OF MEAN
YES	12	612.92	175.944	50.791
NO	38	652.32	159.808	25.924

Mean cortisol level in cases with coronary artery disease are 612.92 and in cases without coronary artery disease are 652.32

TABLE : 9. MEAN CORTISOL LEVEL IN CASES WITH AND WITHOUT CORONARY ARTERY DISEASE

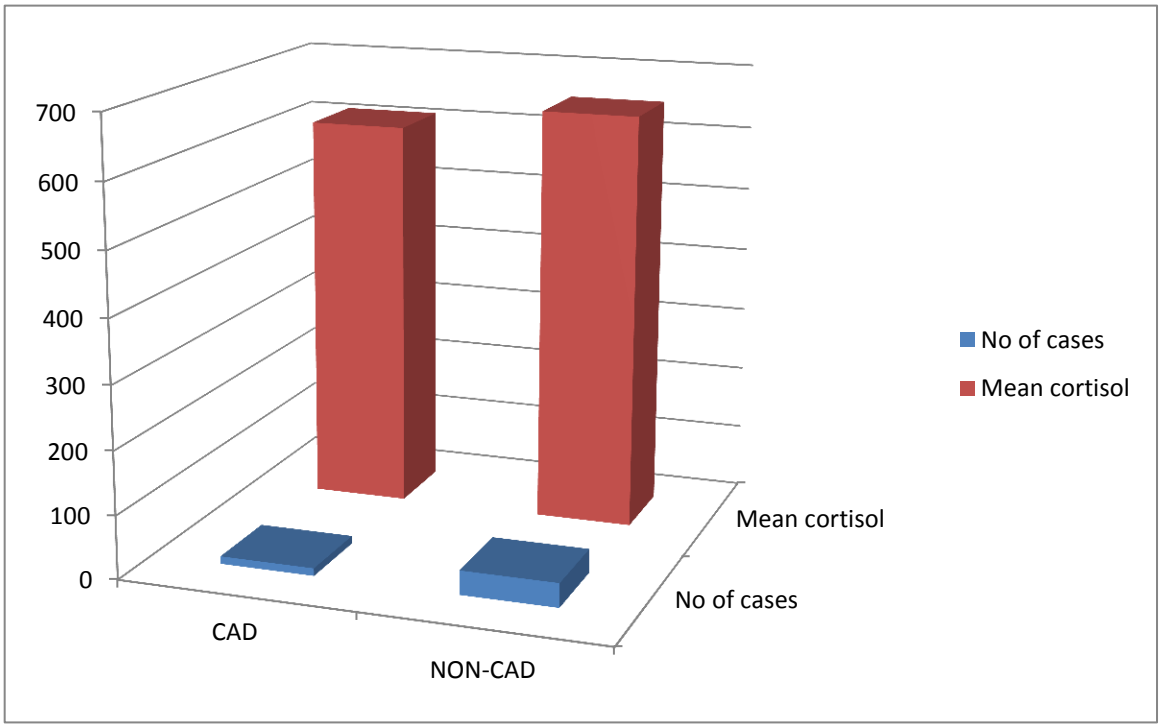


TABLE: 10. NUMBER OF CASES WITH NORMAL AND ELEVATED SYSTOLIC BLOOD PRESSURE

	NUMBER OF CASES	**PERCENTAGE**
SYSTOLICBP <140mmHg	13	26
SYSTOLIC BP >/=140mmHg	37	74
TOTAL	50	100.0

Of the 50 cases 13 had systolic BP less than 140mmHg , 37 had systolic BP more than or equal to 140mmHg.ie., 26 percent had normal systolic blood pressure and 74 percent had elevated systolic blood pressure

CHART : 10. NUMBER OF CASES WITH NORMAL AND ELEVATED SYSTOLIC BLOOD PRESSURE

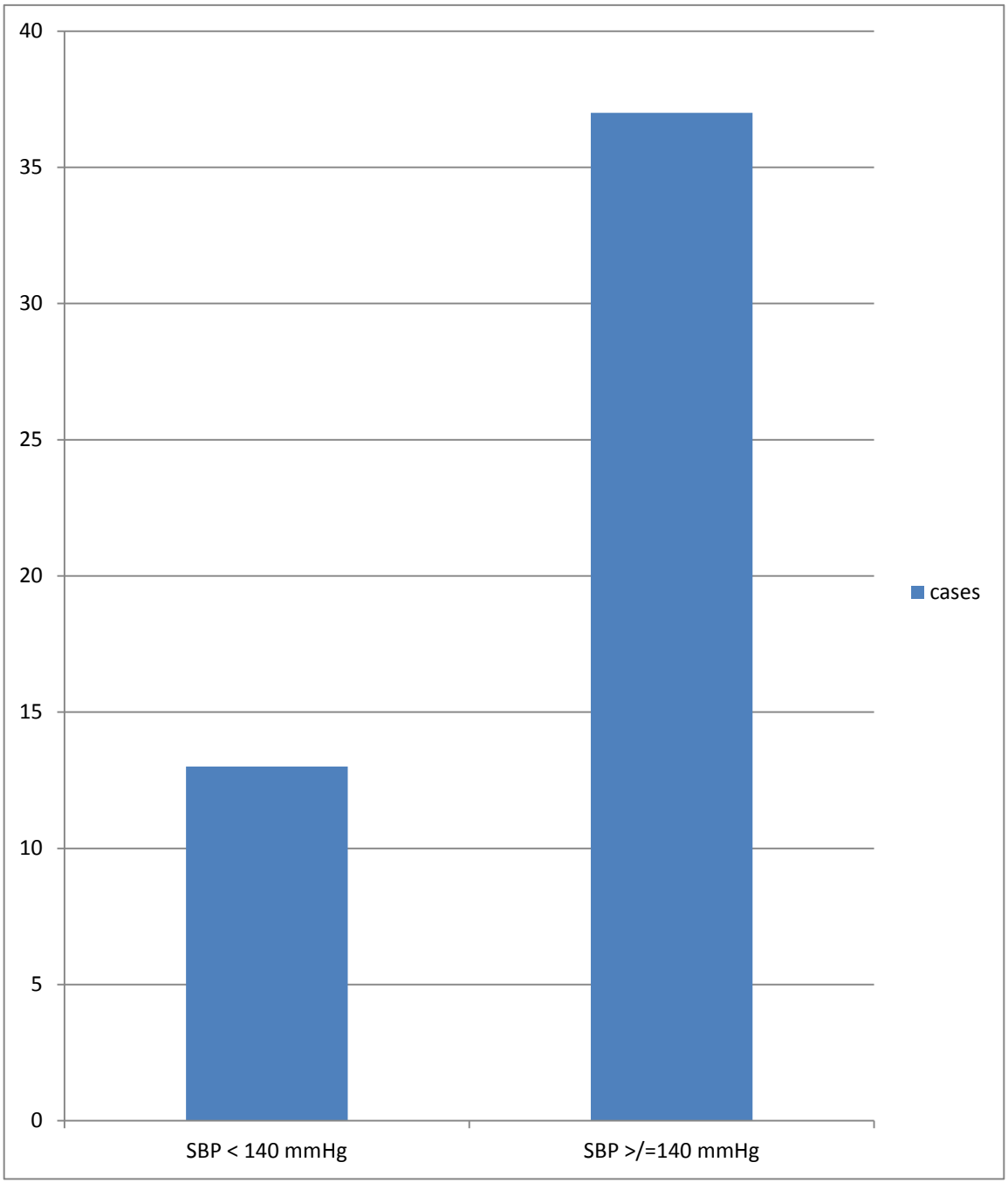


TABLE : 11. NUMBER OF CASES WITH NORMAL AND ELEVATED DIASTOLIC BLOOD PRESSURE

	NUMBER OF CASES	PERCENTAGE
DIASTOLIC BP< 90 mmHg	35	70
DIASTOLIC BP >/=90mmHg	15	30
TOTAL	50	100.0

Of the 50 cases , 35 had diastolic BP less than 90 mmHg and 15 had diastolic BP more than or equal to 90 mmHg.ie., 70 per cent had normal diastolic BP and 30 percent had elevated diastolic BP

CHART :11. NUMBER OF CASES WITH NORMAL AND ELEVATED DIASTOLIC BLOOD PRESSURE

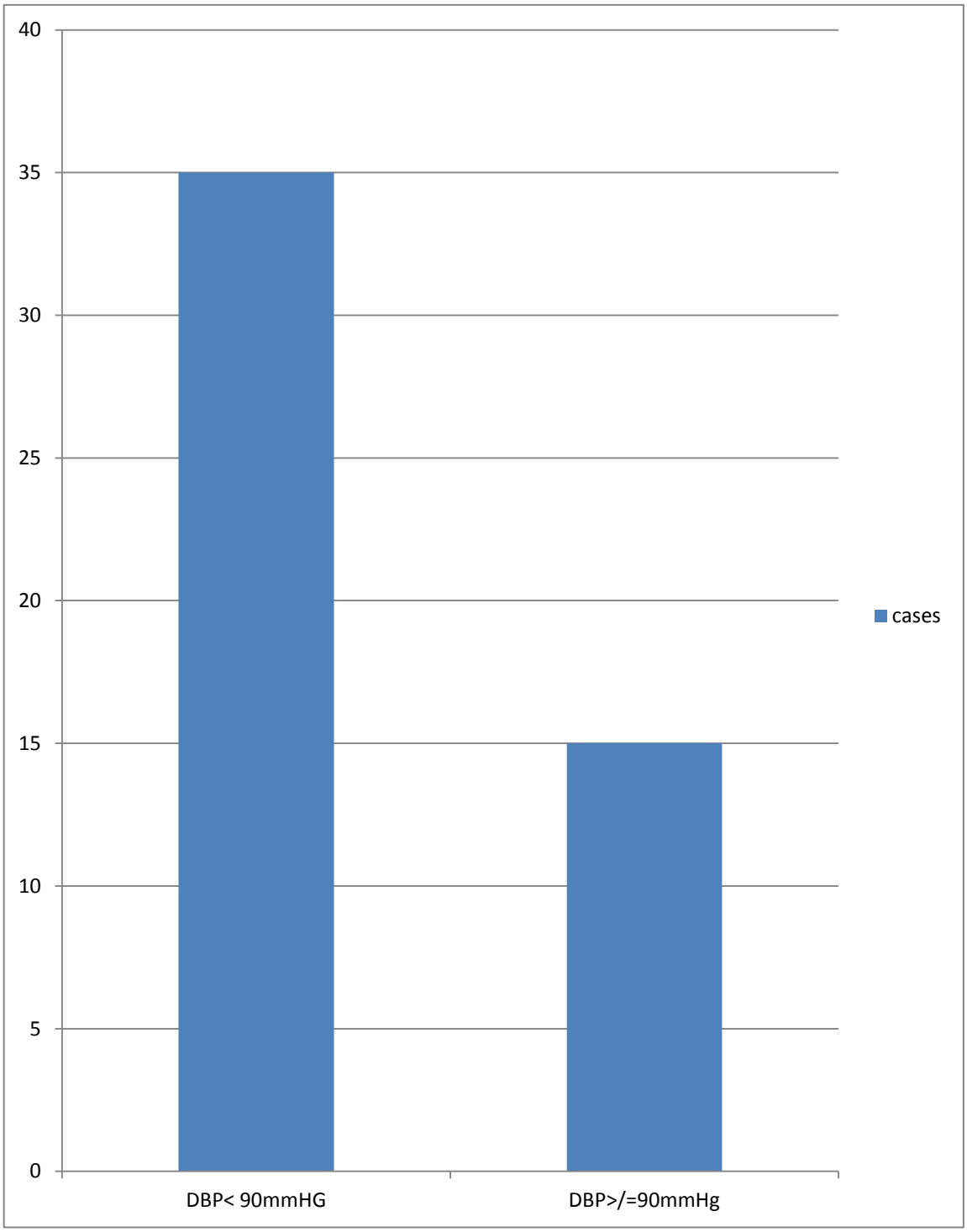


TABLE : 12. NUMBER OF CASES WITH NIHSS SCORE LESS THAN OR EQUAL TO 6 AND GREATER THAN 6:

	NUMBER OF CASES	**PERCENTAGE**
NIHSS</=6	15	30
NIHSS>6	35	70
TOTAL	**50**	**100.0**

Of the 50 cases, 15 had NIHSS score less than or equal to 6 and 35 had NIHSS score more than 6.ie., 30 % had NIHSS less than or equal to 6 and 70 % had NIHSS more than 6

CHART : 12. NUMBER OF CASES WITH NIHSS SCORE LESSS THAN OR EQUAL TO 6 AND GREATER THAN 6:

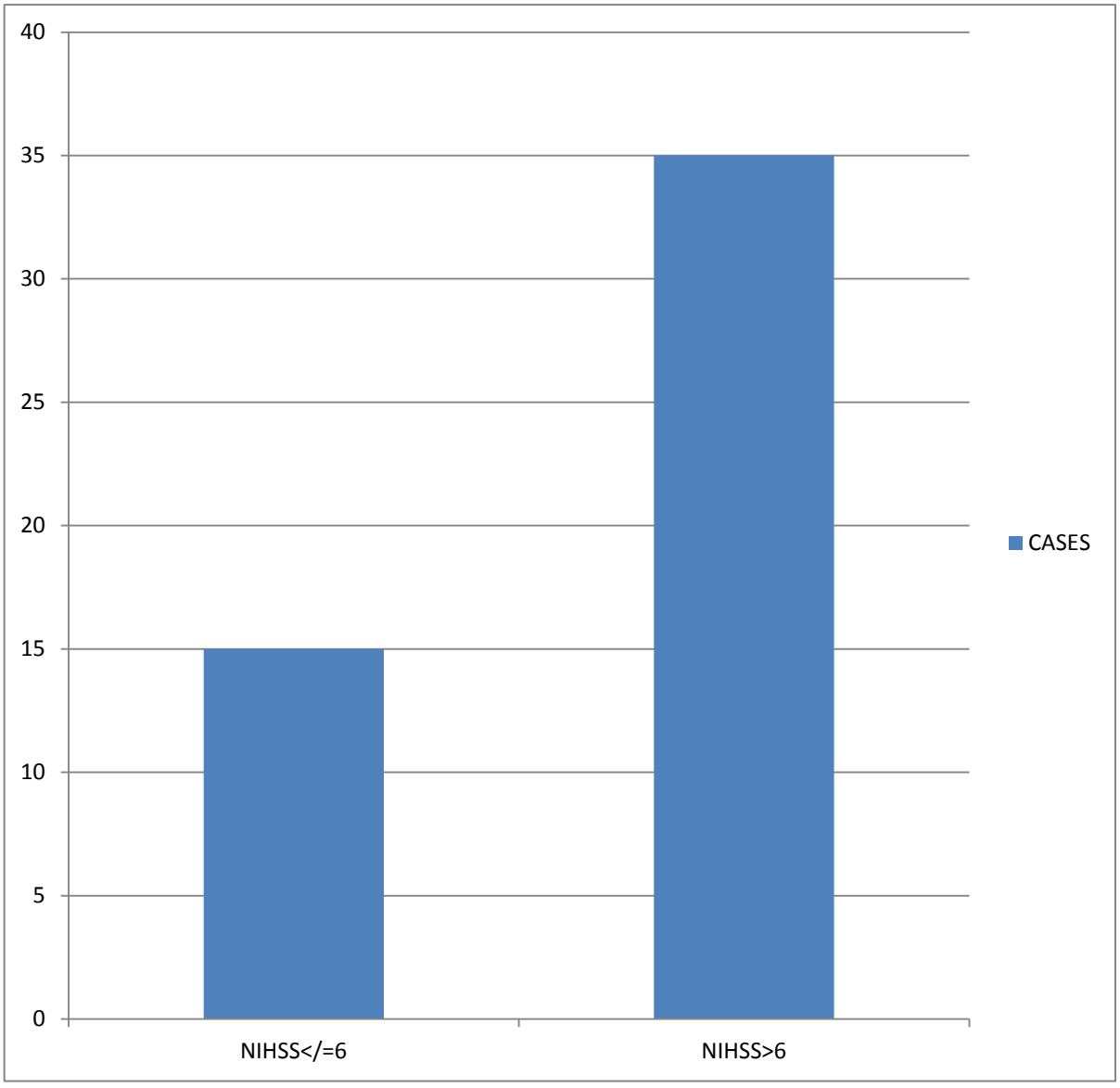


TABLE : 13. NUMBER OF CASES BASED ON MODIFIED RANKIN SCALE LESS THAN OR EQUAL TO 3 AND MORE THAN 3

	NUMBER OF CASES	**PERCENTAGE**
MRS </=3	19	38.0
MRS>3	31	62.0
TOTAL	50	100.0

Of the 50 cases 19 had Modified Rankin scale of less than or equal to 3 after 15 days and 31 had Modified Rankin Scale of more than 3 after 15 days.ie.,38 percent had MRS</=3 and 62 percent had MRS >3 .

CHART : 13. NUMBER OF CASES BASED ON MODIFIED RANKIN SCALE LESS THAN OR EQUAL TO 3 AND MORE THAN 3

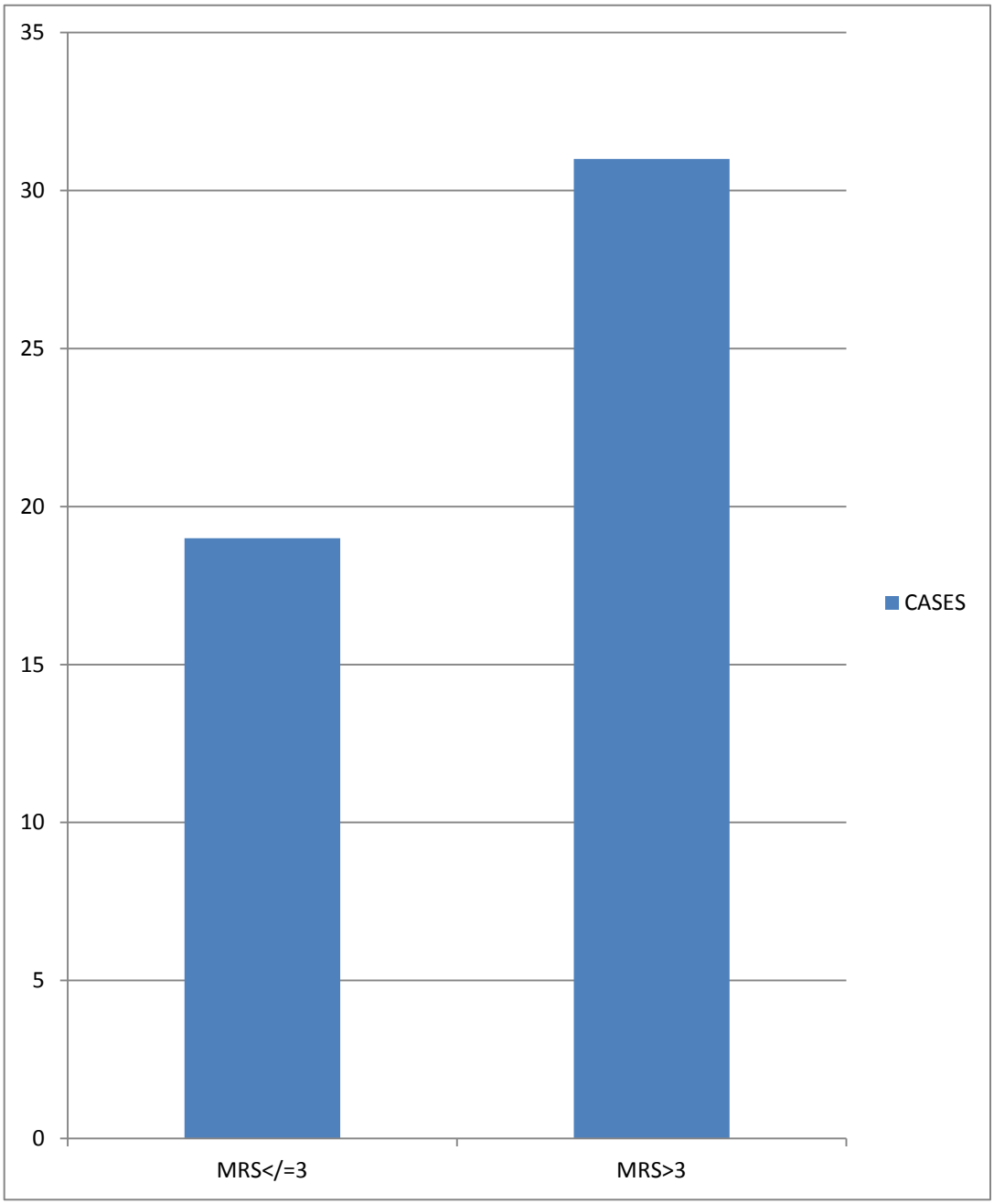


TABLE : 14. NUMBER OF CASES WITH NORMAL AND ELEVATED SERUM CORTISOL

	NUMBER OF CASES	**PERCENTAGE**
SERUM CORTISOL </=690nmol/L	23	46
SERUM CORTISOL>690nmol/L	27	54
TOTAL	**50**	**100.0**

Of the 50 cases , 23 had normal serum cortisol of less than or equal to 690 nmol/L and 27 had elevated serum cortisol of more than 690 nmol/L.ie., 46 percent had normal serum cortisol levels and 54 percent had elevated serum cortisol levels

CHART : 14. NUMBER OF CASES WITH NORMAL AND ELEVATED SERUM CORTISOL

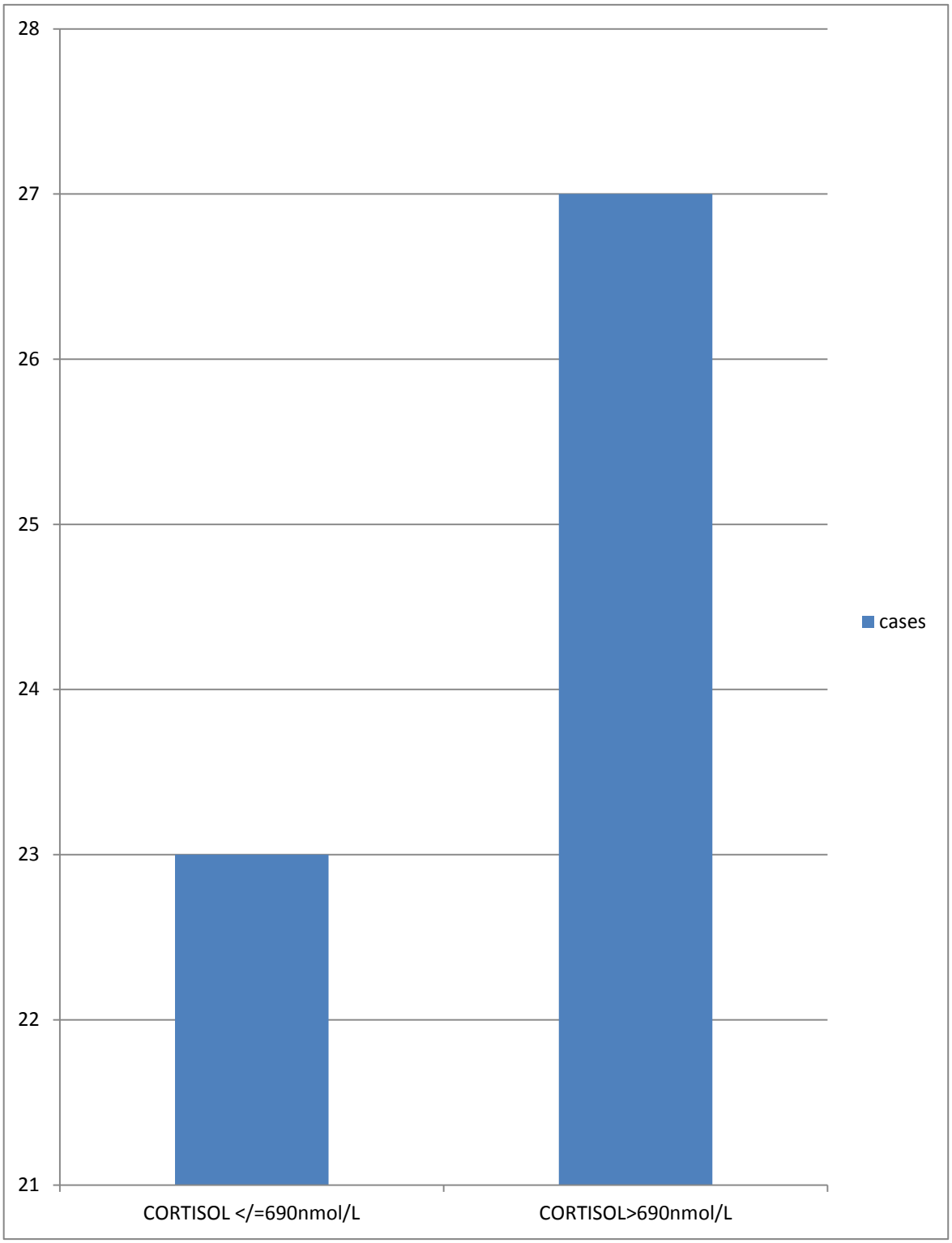


TABLE :15. DISTRIBUTION OF CASES BASED ON TERRITORY OF IINFARCT

	NUMBER OF CASES	**PERCENTAGE**
ACA	6	12.0
MCA	42	84.0
PCA	2	4.0
TOTAL	**50**	**100.0**

Of the 50 cases, 6 had infarct in the Anterior cerebral artery territory and 42 had infarct in the middle cerebral artery territory and 2 had infarct in the posterior cerebral artery territory.ie., 12 percent had ACA territory infarct, 42 percent had MCA territory infarct, 2 percent had PCA territory infarct.

CHART :15. DISTRIBUTION OF CASES BASED ON TERRITORY OF IINFARCT

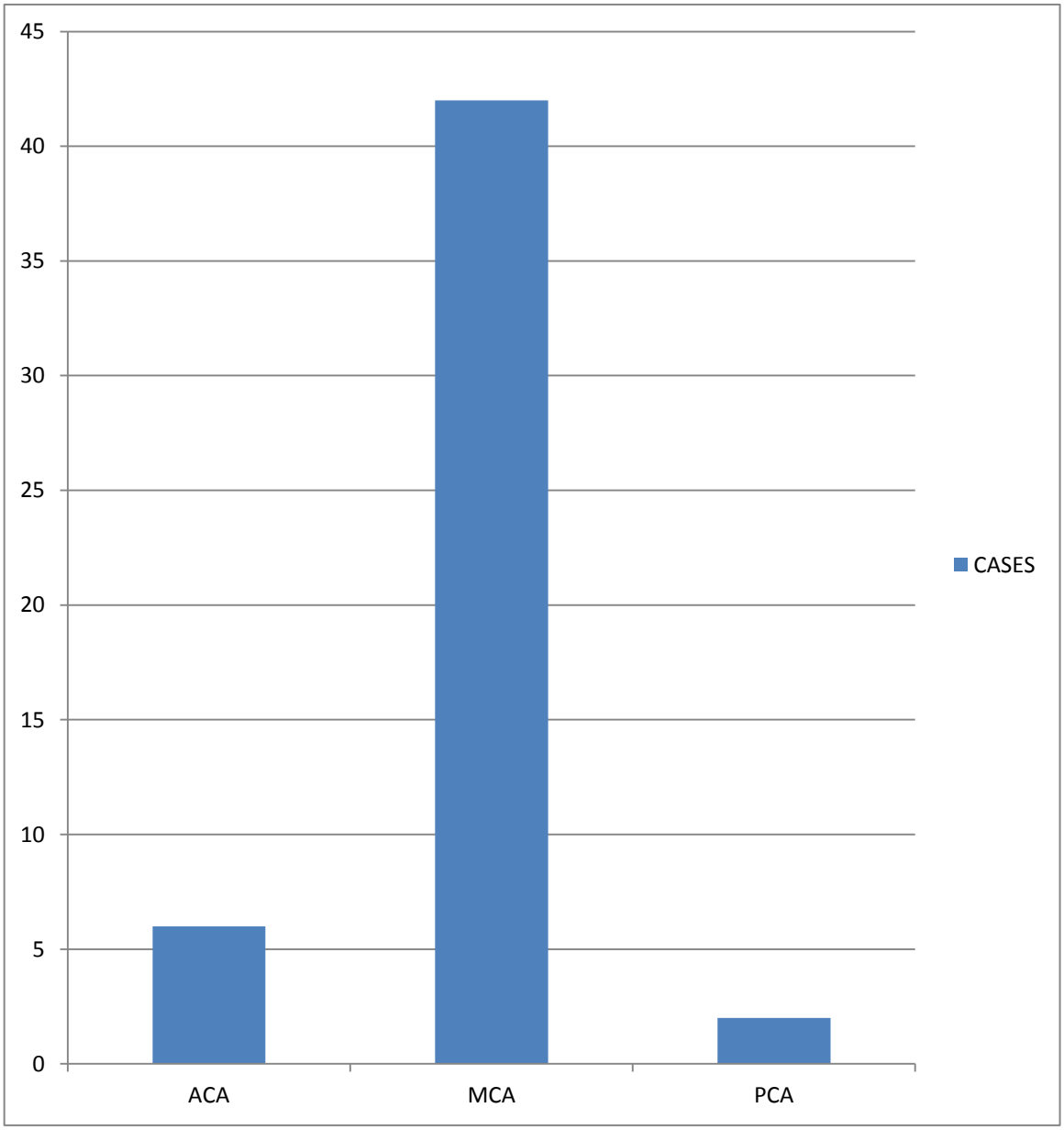


TABLE : 16. CORRELATION OF SERUM CORTISOL LEVELS AND NIHSS SCORE

NIHSS SCORE ON ADMISSION	SERUM CORTISOL IN NMOL/L			
	</= 690		>690	
	NO OF CASES	PERCENTAGE	NO OF CASES	PERCENTAGE
Less than or equal to 6	15	65.2	0	0
More than 6	8	34.8	27	100
TOTAL	**23**	**100**	**27**	**100**

Of the 50 cases, serum cortisol level of 23 cases were less than or equal to 690nmol/L, of which 15 cases had NIHSS score of less than or equal to 6 and 8 had NIHSS score of more than 6 . Of the cases with serum cortisol of less than or equal to 690nmol/L ,65.2% had NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6 . Remaining 27 cases had serum cortisol level more than 690 nmol/L and their NIHSS score was above 6. 100% of the cases with serum cortisol level of more than 6 had NIHSS score above 6.With the p value of <0.001 this is found to be statistically significant.

CHART : 16. CORRELATION OF SERUM CORTISOL LEVELS AND NIHSS SCORE

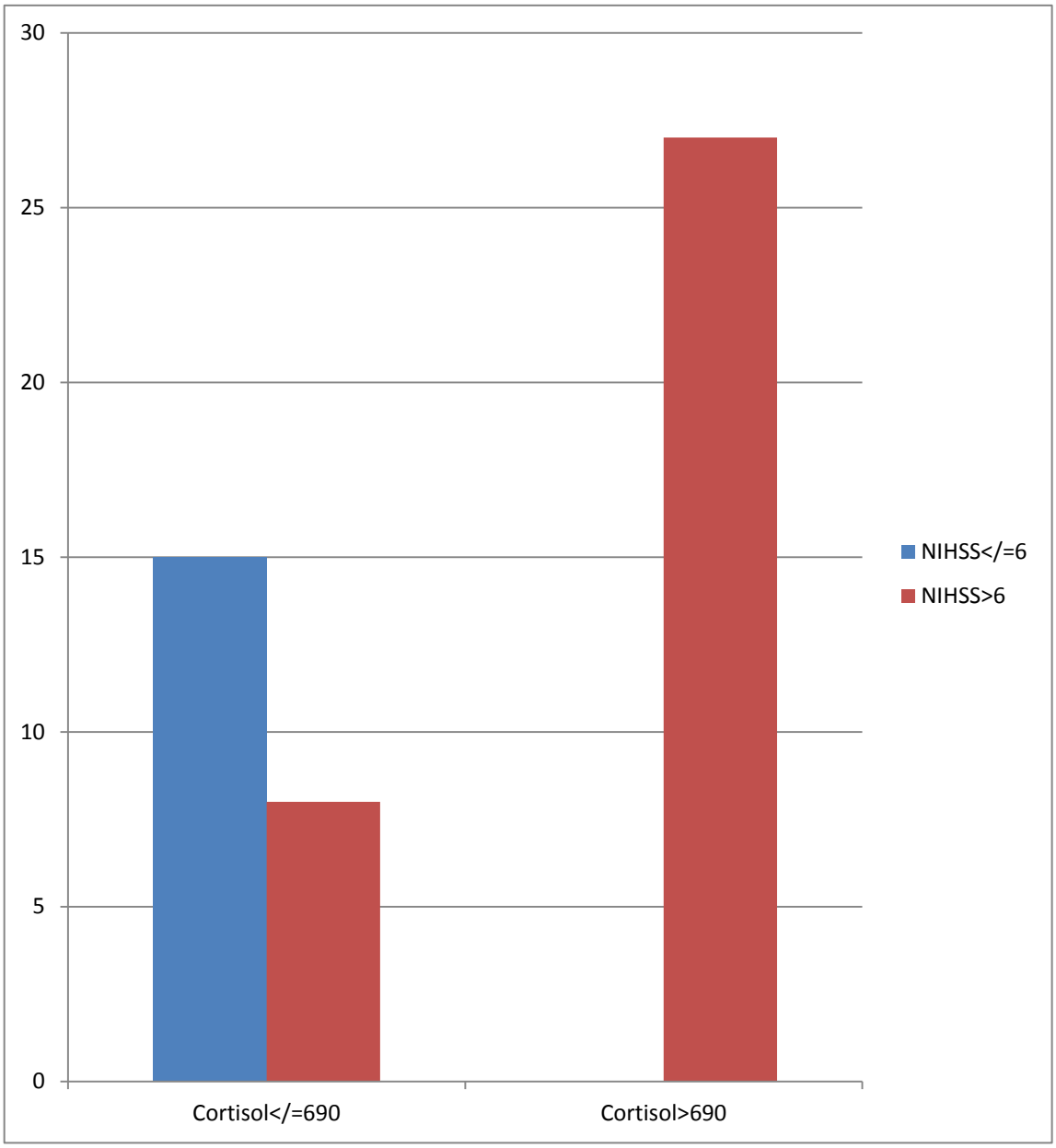
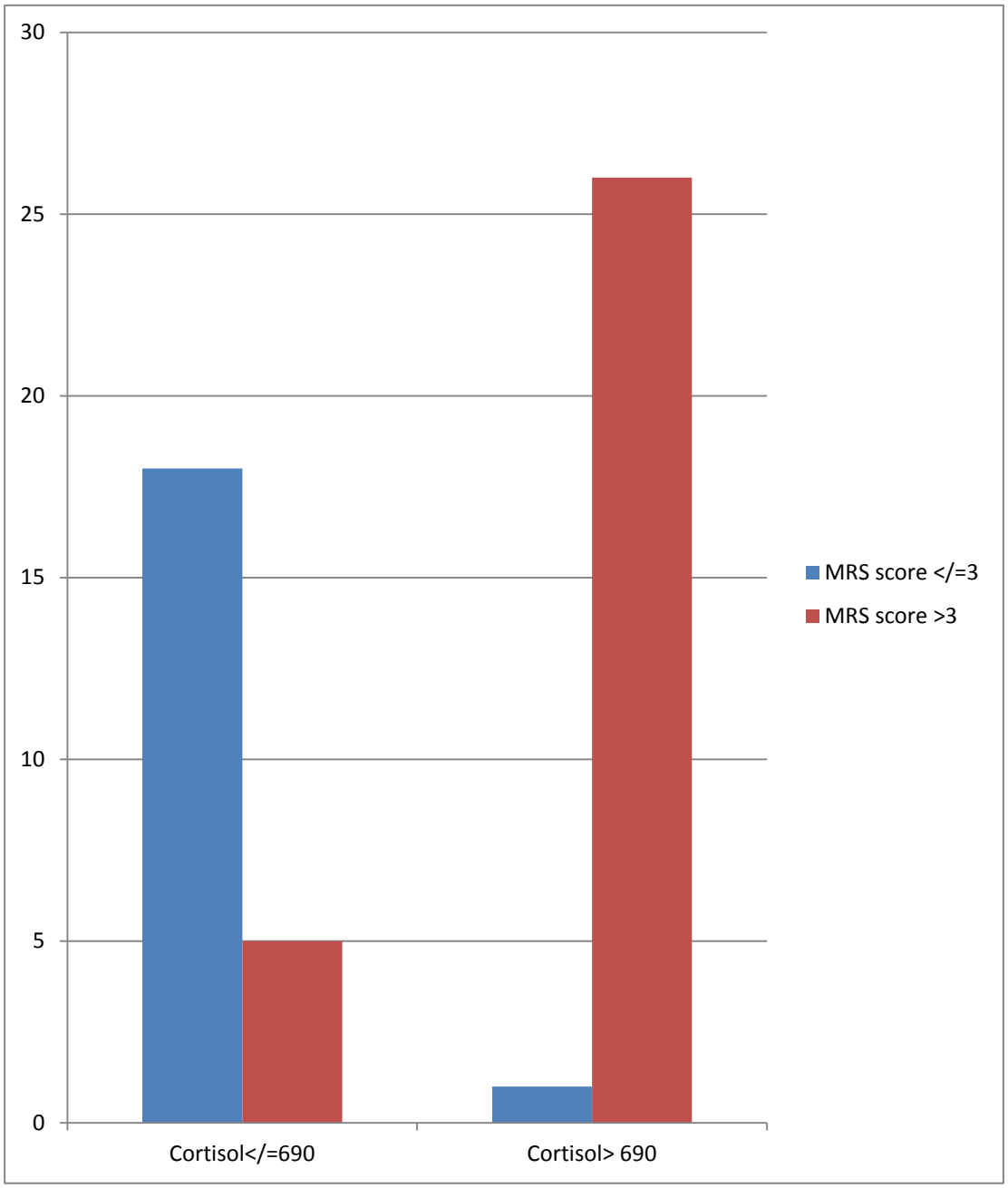


TABLE: 17. CORRELATION OF SERUM CORTISOL LEVELS WITH MODIFIED RANKIN SCALE

MRS SCORE	SERUM CORTISOL IN nmol/L			
	</= 690		>690	
	No of cases	Percentage	No of cases	Percentage
Less than or equal to 3	18	78.3	1	3.7
More than 3	5	21.7	26	96.3
TOTAL	23	100	27	100

Of the 50 cases, serum cortisol levels of 23 cases were less than or equal to 690nmol/L,of which18 had MRS score, which is measured after 15 days , of less than or equal to 3 and 5 had MRS score of more than 3.Of the cases which had serum cortisol level less than or equal to 690 nmol/L, 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3.And in the remaining 27 cases which had serum cortisol level more than 690 nmol/L 1 case had MRS score of less than or equal to 3(3.7%) and 26(96.3%) cases had MRS score of more than 3.With the p value of <0.001, this is statistically significant

CHART: 17. CORRELATION OF SERUM CORTISOL LEVELS WITH MODIFIED RANKIN SCALE



DISCUSSION:

A total of 50 patients were enrolled in the study who were proven to have Acute Ischemic Stroke by CT Brain which was taken at the time of admission. The minimum age of the patients is 31 years and the maximum age was 85 years. Among the 50 patients ,38 % of the acute ischemic stroke occurred in the age group of 61 to 70 years. And about 58 %were males and 42 % were females.

The mean cortisol level was 631.07 in males.The mean cortisol level in females was 659.14

Of the 50 cases, 26% were diabetics and 74% were non diabetics. The mean cortisol level in diabetics was 590.15 7. The mean cortisol level in non diabetics was 661.38

40 percent were hypertensives and 60 percent were normotensives. The mean cortisol level in hypertensives was 657.75. The mean cortisol level in normotensives was 632.93

24 % had CAD and 76 % did not have CAD. The mean cortisol level in cases with CAD was 612.92 The mean cortisol level in non CAD was 652.32 .

Of the 50 cases 13 had systolic BP less than 140mmHg , 37 had systolic BP more than or equal to 140mmHg.ie., 26 percent had normal systolic blood pressure and 74 percent had elevated systolic blood pressure.Also, 35 had diastolic BP less than 90 mmHg and 15 had diastolic BP more than or equal to 90 mmHg.ie., 70 per cent had normal diastolic BP and 30 percent had elevated diastolic BPOf the 50 cases, 6 had infarct in the Anterior cerebral artery territory and 42 had infarct in the middle cerebral artery territory and 2 had infarct in the posterior cerebral artery territory.ie., 12 percent had ACA territory infarct, 42 percent had MCA territory infarct, 2 percent had PCA territory infarct. It is clear that majority of the cases had MCA territory infarct Of the 50 cases, serum cortisol level of 23 cases were within normal limits (</=690nmol/L) of which 65.2% had NIHSS score of less than or equal to 6 and 34.8% of the cases had NIHSS score more than 6 .As the NIHSS score of less than or equal to 6 is considered to be a minor stroke, it is obvious from the above findings that most of the cases with normal cortisol level had no major stroke.

Remaining 27 cases had elevated serum cortisol levels.100% of the cases with serum cortisol level of more than 690nmol/L had NIHSS score above 6.With the p value of <0.001 this is found to be statistically significant. As the NIHSS score above 6 is considered to be moderate to

severe stroke, it is obvious from the above observation that nearly all cases with elevated cortisol level had moderate to severe stroke.

Of the 50 cases, serum cortisol levels of 23 cases were within normal limits(,/=690nmol/L)of which 78.3% had MRS score less than or equal to 3 and 21.7% had MRS score more than 3.Since MRS score is a measure of functional outcome and any score less than or equal to 3 is considered to have a favourable outcome ,it is clear from the above findings that most of the cases with normal serum cortisol had a favourable outcome with minimal neurological impairment.

And in the remaining 27 cases which had serum cortisol level more than 690 nmol/L, 3.7% had MRS score of less than or equal to 3 and 96.3% had MRS score of more than 3.With the p value of <0.001, this is statistically significant .Since MRS score more than 3 is associated with bad outcome, most of the cases with elevated serum cotisol had a poor outcome with severe neurological impairment.

Also among the 50 cases , 5 cases showed mortality who had elevated serum cortisol (>690nmol/L) at the time of admission.

SIMILAR STUDIES:

A study done by *Marklund N et al* showed high cortisol levels predicts poor stroke outcome.This study showed patients with severe functional impairment (n=38, grade 3-4) had higher cortisol levels on day 1 (540+/-330 vs 387+/-253 nmol/L., P<0.05) when compared with the patients of mild symptoms.Also 28 day mortality was significantly predicted by high levels of serum cortisol on day 1.

In a study done by *Wen Jie Zi et al* there is poor outcome in patients with elevated serum cortisol levels on the day of admission (P<0.0001).There was a positive correlation between the NIHSS and serum cortisol levels(P<0.0001)

Similar to the above 2 studies our study also showed positive correlation between serum cortisol levels and NIHSS score as well as MRS score in predicting the severity of the stroke and the functional outcome,which is found to be statistically significant(P<0.001).

Hence it was very clear that acute ischemic stroke was very severe in patients with high serum cortisol levels at the time of admission and also the outcome of the patients after 15 days was poor in patients with high serum cortisol levels.

CONCLUSION:

Among the patients with acute ischemic stroke ,high serum cortisol levels at the time of admission correlates with,

1. Clinical severity which is assessed by National Institute of Health Stroke Scale and
2. Poor prognosis and functional outcome after 15 days which is assessed by Modified Rankin Scale .

CLINICAL SIGNIFICANCE:

In humans, the adrenal stress response causes increased blood glucose, catabolism,heart rate,and potentiates ischemic neuronal damage.In acute ischemic stroke these effects could induce secondary brain damage.Hypothalamo- Pituitary- adrenal axis alterations are one of the major stress induced alterations after the event of cerebral ischemia.

Cortisol is an independent short term marker of prognosis of functional outcome and death in patients with acute ischemic stroke even after the correction of confounding factors.Elevated cortisol after the onset of stroke is clearly associated with morbidity, dependency and mortality.A combined model can however add significant information to the clinical score.

Since early prediction of stroke outcome is very important for allocation of therapeutic strategies, serum cortisol level measurement at the time of admission can add significant predictive information to the existing NIHSS score.

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2. O'Neill PA, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke 1991; 22:842-7.

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PROFORMA

NAME:

UNIT NO.:

I.P.NO.:

AGE/SEX:

OCCUPATION:

ADDRESS:

DATE OF ADMISSION:

DATE OF DISCHARGE:

CONTACT NO:

COMPLAINTS:

PAST HISTORY:

Diabetes/ Hypertension/ Dyslipidemia/ CAD/ CKD/Malignancy/surgery /

Liver diease

DRUG HISTORY:

GENERAL EXAMINATION:

SYSTEM EXAMINATION:

NIHSS SCORING:-

	SCORE
LEVEL OF CONSCIOUSNESS	0-7
HORIZONTAL EYE MOVEMENT	0-2
VISUAL FIELD TEST	0-3
FACIAL PALSY	0-3
MOTOR ARM(right and left)	0-8
MOTOR LEG(right and left)	0-8
LIMB ATAXIA	0-2
SENSORY	0-2
LANGUAGE	0-3
SPEECH	0-2
EXTINCTION & INATTENTION	0-2

SCORE	STROKE SEVERITY
0	NO STROKE SYMPTOMS
1-4	MINOR STROKE
5-15	MODERATE STROKE
16-20	MODERATE-SEVERE STROKE
21-42	SEVERE STROKE

Total score:

CT BRAIN PLAIN:

SERUM CORTISOL:

MODIFIED RANKIN SCALE(ASSESSED AFTER 15 DAYS) FOR FUNCTIONAL OUTCOME:-

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent. 6 – Dead

Total score after 15 days:

NIHSS SCORING:-

1a. Level of Consciousness

0: Alert

1: Not alert, but arousable with minimal stimulation

2: Not alert, requires repeated stimulation to attend

3: Coma

1.b. LOC questions (Ask patient the month and her/his age)

0: Answers both correctly

1: Answers one correctly

2: Both incorrect

1.c. LOC commands (Ask patient to open/close eyes & form/release fist)

0: Obeys both correctly

1: Obeys one correctly

2: Both incorrect

2. Best gaze (only horizontal eye movement)

0: Normal

1: Partial gaze palsy

2: Total gaze paresis or Forced deviation

3. Visual Field testing

0: No visual field loss

1: Partial hemianopia

2: Complete hemianopia

3: Bilateral hemianopia (blind including cortical blindness)

4. Facial Paresis (Ask patient to show teeth/ raise eyebrows & close eyes tightly)

0: Normal symmetrical movement

1: Minor paralysis (flattened nasolabial fold, asymmetry on smiling)

2: Partial paralysis (total or near total paralysis of lower face)

3: Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5. Motor Function – Arm (5a left,

0: Normal (extends arms 90degree **5b right)**

(or 45 degree) for 10 seconds)

1: Drift

2: Some effort against gravity

3: No effort against gravity

4: No movement

9: Untestable (Joint fused or limb amputated)
(*do not add score*)

6. Motor Function - Leg (6a-left 6b-Right)

0: Normal (hold leg in 300 position for 5 sec without drift)

1: Drift

2: Some effort against gravity

3: No effort against gravity

4: No movement

9: Untestable (Joint fused or limb amputated)
(do not add score)

7. Limb Ataxia

0: No ataxia

1: Present in one limb

2: Present in two limbs

8. Sensory (Use pinprick to test arms, legs, trunk and face- compare side to side)

0: Normal

1: Mild to moderate decrease in sensation

2: Severe to total sensory loss

9. Best Language (Ask patient to describe picture, name items, read sentences)

0: No aphasia

1: Mild to moderate aphasia

2: Severe aphasia

3: Mute

10. Dysarthria (Ask patient to read several words)

0: Normal articulation

1: Mild to moderate slurring of words

2: Near unintelligible or unable to speak

9: Intubated or other physical barrier (do not add score)

11. Extinction and inattention (Formerly Neglect) (Use visual or sensory double stimulation)

0: Normal

1: Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities

2: Severe hemi-inattention or hemi-inattention to more than one modality

Total Score (0-42):

ABBREVIATION

ACTH	-	Adrenocorticotrophic Harmone
ASD	-	Atrial Septal defect
CBG	-	Cortisol Binding Globulin
CBF	-	Cerebral Blood Flow
CN	-	Coagulation Necrosis
CRH	-	Cortisotrophin Releasing harmone
CYP	-	Cytochrome P 450
DIVC	-	Disseminated Inravascular Coagulation
DNA	-	Deoxyribo Nucleic Acid
EEG	-	Electro Encephalo Gram
HDL	-	High Density Lipoprotein
HPA	-	Hypothalamo Pituitary Adrenal Axis
IP	-	Ischemic Penumbra
ITT	-	Insulin Tolerance Test
LDL	-	Low Density Lipoprotein

LSD	-	Lysergic Acid Derivative
MCA	-	Middle Cerebral Artery
NMDA	-	N-methyl-d-Aspartate
NO	-	Nitric oxide
RHD	-	Rheumatic Heart Disease
RR	-	Relative Risk
SAH	-	Hemorrhage
SWD	-	Spontaneous Wave Depolarisation
TIA	-	Transient Ischemic Attack
TSH	-	Thyroid Stimulaing Harmone

S. NO	NAME	AGE	SEX	DIABETES	HYPERTENSION	CAD	SYTOLIC BP	DIASTOLIC BP	NIHSS SCORE ON ADMISSION	SERUM CORTISOL (NMOL/L	CT BRAIN- TERRITORY OF INFARCT	MODIFIED RANKIN SCALE AT 15 DAYS
1	MANI	50	MALE	YES	NO	YES	150	90	4	331	ACA	2
2	VELU	52	MALE	NO	NO	YES	140	80	6	413	MCA	3
3	GANESAN	70	MALE	NO	YES	YES	140	90	7	696	MCA	4
4	RAJA	63	MALE	NO	YES	NO	150	90	7	687	MCA	4
5	GANESAN	52	MALE	NO	NO	NO	140	90	9	709	MCA	5
6	MANGALESHWARAN	65	MALE	NO	NO	YES	160	80	8	714	MCA	4
7	RAJASEKAR	65	MALE	NO	NO	NO	160	100	11	772	MCA	5
8	GAJENDRAN	60	MALE	NO	NO	NO	120	80	8	689	MCA	4
9	MEENATCHI	70	FEMALE	NO	NO	NO	160	100	10	757	MCA	2
10	RAMACHANDRAN	51	MALE	NO	YES	NO	160	80	8	691	MCA	4
11	KALYANAM	78	MALE	NO	NO	YES	120	80	7	627	MCA	3
12	GNANAM	52	MALE	YES	NO	NO	150	100	9	698	MCA	4
13	SHANMUGAM	61	MALE	NO	NO	YES	170	100	12	744	MCA	5
14	BASKAR	68	MALE	NO	YES	YES	110	70	7	677	MCA	4
15	MARIMUTHU	85	MALE	NO	NO	NO	110	70	6	435	MCA	3
16	CHANDRAN	67	MALE	NO	NO	NO	150	80	8	711	MCA	4
17	KUMARASAMY	66	MALE	YES	YES	YES	160	110	12	772	MCA	5
18	MUNUSAMY	47	MALE	YES	NO	N0	160	100	11	761	MCA	5
19	BALASUBRAMANIAM	54	MALE	NO	YES	NO	140	90	7	680	MCA	4
20	SHANKAR	50	MALE	NO	NO	NO	110	80	4	358	ACA	2
21	VENKATESAN	70	MALE	NO	NO	NO	150	100	8	693	MCA	4
22	JEYARAMAN	75	MALE	NO	NO	NO	110	70	6	438	MCA	3
23	JOHN BOSCO	75	MALE	YES	YES	NO	110	70	4	386	MCA	2
24	THANTHONI	55	MALE	NO	NO	NO	180	100	18	827	MCA	6
25	GUBENDRAN	68	MALE	NO	YES	NO	110	80	7	678	MCA	4
26	SAMYNATHAN	59	MALE	NO	NO	NO	140	90	8	707	MCA	4
27	POONGODI	38	FEMALE	NO	YES	NO	180	110	19	993	MCA	6
28	SELVARAJ	65	MALE	NO	YES	NO	160	80	7	641	MCA	3
29	ELUMALAI	34	MALE	NO	NO	NO	140	80	5	496	PCA	2
30	SUNDARAJ	72	MALE	NO	YES	NO	160	80	8	691	MCA	4
31	ALAMELU	70	FEMALE	YES	YES	NO	150	90	9	717	MCA	4
32	CHANDRA	50	FEMALE	NO	NO	NO	170	100	11	786	MCA	5
33	ELLAMALI	70	FEMALE	NO	YES	NO	110	70	5	524	MCA	2
34	MALLIGA	80	FEMALE	NO	NO	NO	140	80	8	733	MCA	4
35	NEELA	65	FEMALE	YES	YES	NO	110	70	4	317	ACA	2
36	MARAGATHAMMAL	73	FEMALE	YES	YES	NO	150	90	8	730	MCA	4
37	AMARAVATHI	70	FEMALE	NO	NO	NO	110	70	4	347	ACA	2
38	KANNAMA	83	FEMALE	NO	NO	NO	160	100	18	869	MCA	6
39	ANNAMAL	75	FEMALE	NO	YES	NO	170	110	19	965	MCA	6
40	SUSEELA	82	FEMALE	YES	YES	YES	160	80	8	712	MCA	4
41	SIVABAKYAM	63	FEMALE	YES	NO	YES	150	90	5	539	ACA	2
42	VALLIAMMAL	80	FEMALE	NO	YES	NO	150	90	7	716	MCA	4
43	ANDALAMMAL	80	FEMALE	YES	NO	YES	180	120	16	827	MCA	6
44	BAYAMMAL	65	FEMALE	NO	NO	NO	140	80	7	555	MCA	3
45	THARA RANI	82	FEMALE	NO	NO	NO	110	70	8	713	MCA	4
46	SUMATHI	31	FEMALE	NO	NO	NO	120	80	6	466	MCA	3
47	RAMAN	80	MALE	YES	YES	NO	140	80	6	579	PCA	3
48	JABEEN	80	FEMALE	YES	YES	YES	150	100	4	303	ACA	2
49	VENDAMAAL	60	FEMALE	NO	NO	NO	140	90	7	693	MCA	4
50	KAMALA	65	FEMALE	NO	NO	NO	150	100	5	580	MCA	2

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.1589/ME-1/Ethics/2014 Dt:06.03.2014.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on correlation between serum cortisal and severity of acute ischemic stroke in patients admitted in Govt. Kilpauk Medical College Hospital, Chennai" – For Project Work submitted by Dr.T.Allwyn Yabesh, MD (GM), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

CHAIRMAN, 29/5/14.
Ethical Committee
Govt.Kilpauk Medical College,Chennai

GOVT. KILPAUK MEDICAL COLLEGE
29 MAY 2014
Kilpauk, Chennai-10.